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ARCHIVES OF SURGERY

VOLUME 15 DECEMBER, 1927 NUMBER 6

PITUITARY ADAMANTINOMAS

REPORT OF THREE CASES *

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Pituitary adamantinomas are solid or cystic, benign or local malignant tumors. They contain enamel or enamel-forming tissue and develop from epithelial rests of the embryonic hypophyseal duct. Several types of tumors or tumor cysts have been described in the sella and the suprasellar regions, and much confusion has arisen regarding their classification and etiology. Some uniformity of nomenclature is slowly appearing, however, and today the classifications of certain types of tumors and their origins are generally accepted. Thus the most common tumor of the hypophysis is now regarded as an adenoma, while the cysts are believed to develop from embryologic remnants of the hypophyseal duct proper or from its extreme upper portion, the pouch of Rathke. Cysts or tumors arising from the duct are distinguished from those originating in Rathke's pouch by the squamous epithelium of the former contrasted with the cylindric, frequently ciliated, epithelial lining of the latter. Some authors still use the terms, "Rathke's pouch tumor" and "hypophyseal duct tumor" or "craniopharyngeal duct tumor" as synonymous, but there is a definite histologic distinction, and its general recognition will help materially to overcome the still prevalent confusion.

The exact embryologic anlage of the various cysts or tumors of the hypophyseal region is not only of academic interest, but of distinct clinical value. The cysts arising from Rathke's pouch develop between the anterior and posterior lobes of the pituitary and are, therefore, primarily intrasellar in origin. On the other hand, tumors of the hypophyseal duct, because of the rotation of the pituitary during its development, may occur at any point from the tuber cinereum at the base of the third ventricle, downward along the infundibulum to the anterior hypophyseal lobe. Erdheim [1] has shown that epithelial cell

* From the Department of Surgery, University of Michigan.

1. Erdheim, J.: Zur normalen und pathologischen Histologie der Glandula thyreoidea, parathyreoidea und Hypophysis, Beitr. z. path. Anat. u. z. allg. Pathol. **33**:158, 1903; Ueber Hypophysenganggeschwülste und Hirncholesteatome, Sitzungsb. d. k. Akad. d. Wissensch. Math.-Naturw. Cl., Wien. **113**:537, 1904; Ueber einen neuen Fall von Hypophysenganggeschwulst, Centralbl. f. allg. Pathol. u. path. Anat. **17**:209 (March 31) 1906.

rests, remnants of the hypophyseal duct, can be demonstrated in 80 per cent of normal adults. These occur chiefly at two sites; an upper group is situated on the anterior aspect of the infundibulum near the third ventricle, and a lower group at the angle between the infundibulum and the anterior lobe. The majority of tumors of the hypophyseal duct found at operation or necropsy have originated in one or the other of these two locations.

Compared to the pituitary adenomas, the squamous epithelial tumors originating in the hypophyseal duct are relatively rare, only about sixty cases being recorded. These may be divided histologically, according to Duffy,[2] into three groups; first, the benign papillary cyst or intracystic papilloma; second, the benign or locally malignant adamantinoma which may be calcified or uncalcified, cystic or solid, the more complicated adamantinomas, the "authochthonous teratomas" of Ewing and the rarer tumors which resemble the cutaneous epithelioma; third, the rare spindle cell carcinoma with a tendency to metastasize.

The adamantinomas are the most common, comprising possibly half of the tumors originating in the hypophyseal duct. The resemblance between these tumors and those of the jaw was first noted by Onanoff [3] in 1892. Luschka,[4] in 1860, had found nests of squamous epithelium adjacent to the pituitary, but it remained for Erdheim in 1904 to suggest that these groups of epithelial cells were remnants of the embryonic hypophyseal-pharnygeal duct, and that the pituitary adamantinomas were in reality tumors of this origin. He coined the term "Hypophysenganggeschwülste" (tumor of the hypophyseal duct), which is now in general use.

The clinical picture varies with the exact location of the tumor, although nearly all show symptoms of hypopituitarism. The majority show obesity, many presenting the classic picture of the Fröhlich syndrome, designated by Bartels [5] as "dystrophia adiposogenitalis." Infantilism without adiposity (type Lorain) is occasionally observed. Neither gigantism nor acromegaly has been associated with an adamantinoma.

The general symptoms also vary with the age of onset. The two types just noted appear before puberty. In older patients who have

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2. Duffy, William C.: Hypophyseal Duct Tumors: A Report of Three Cases and a Fourth Case of Cyst of Rathke's Pouch, Ann. Surg. **72**:537 (Nov.) 1920.

3. Onanoff, Jacques: Sur un cas d'epithelioma (étude histologique), Paris, 1892.

4. Luschka, Hubert: Der Hirnanhang und die Steissdrüse des Menschen, Berlin, 1860.

5. Bartels, M.: Ueber Plattenepithelgeschwülste der Hypophysengegend (des infundibulums), Ztschr. f. Augenh. **16**:407 and 530, 1906; Ueber die Beziehungen von Veränderungen der Hypophysengegend zu Misswachstum und Genitalstörungen (Dystrophia adiposo-genitalis), München. med. Wchnschr. **55**:201 (Jan. 28) 1908.

developed normally, the growth of the tumor tends to reverse the secondary sexual characteristics. In a man the hair of the face and body gradually becomes scant, and shaving is seldom or never necessary. The pubic hair tends to assume the horizontal feminine form. There is a diminution of sexual vigor, which may progress to complete loss. In women, amenorrhea is frequenly the earliest symptom. The axillary hair usually becomes thin or may disappear entirely. Libido decreases or is absent.

The two sexes are about equally affected. The age incidence is earlier than that for pituitary adenomas, the greatest number of cases occurring in the second decade. Few are reported before the tenth year, probably because the growth of the tumor is usually slow. After the age of 30, the incidence rapidly decreases, although one case was reported at 57 and another at 60. The mortality with and without operation has been high.

Drowsiness was a marked symptom in the majority of cases. In a series compiled by Critchley and Ironside,[6] it was noted in ten of fifteen cases. The excessive lethargy is apparently not related to the degree of adiposity or to the hydrocephalus found in some cases. The basal metabolic rate has not been recorded in the cases reviewed in the literature, but in my patients it was definitely subnormal. It is possible that the excessive drowsy condition so frequently observed may be indirectly due to the subnormal metabolism. No patient showed glycosuria, nor have the patients in previously recorded cases had polyuria. However, one of my patients apparently developed a temporary diabetes insipidus. Only a few determinations of the blood sugar have been recorded. These showed a low blood sugar with an increased sugar tolerance.

The changes in the ocular fundus vary with the location of the primary growth. If it develops at the angle of the infundibulum and the anterior pituitary lobe or beneath the capsule of the latter, the tumor lies below and usually in front of the optic chiasm. Growth of the tumor will, therefore, press on the under surface of the optic nerves and chiasm, producing defects in the upper quadrant of the visual fields. If the growth is most pronounced in the midportion, bitemporal hemianopsia results. Not infrequently, however, the growth tends to pass more to the right or to the left, producing left or right homonymous hemianopsia or blindness in one eye and a temporal hemianopsia in the other, depending on whether the pressure was greatest on the optic nerve behind or in front of the chiasm and on the degree of pressure on the latter. Primary optic atrophy is the rule in these suprasellar, subchiasmal lesions.

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6. Critchley, Macdonald; and Ironside, Redvers, N.: The Pituitary Adamantinomata, Brain **49**:437 (Dec.) 1926.

Tumors developing from the upper group of cell rests may grow first either upward or downward or equally in both directions. If the greater pressure is exerted upward, the third ventricle is early involved, and partial or complete obstruction of the foramina of Monro with a corresponding degree of hydrocephalus results. Choking of the optic disks will then occur. The visual fields show simply contraction. A definite diagnosis by the changes in the disks and visual fields alone is impossible, but these taken in consideration with possible endocrine disturbances make a tentative diagnosis possible. If the roentgenogram shows calcification above the sella, then one can be certain of the location of the lesion and of its probable nature.

When the primary growth of the tumor is downward, primary optic atrophy instead of papilledema will be found. The chiasm is pushed downward and forward. Defects in the lower quadrant of the visual field appear, and finally bitemporal or homonymous hemianopsia, depending on the exact position of the downward pressure, occurs. As in the subchiasmal lesions, the process will eventually progress to total blindness unless the pressure is relieved.

Pressure upward into the third ventricle and downward on the chiasm and optic nerves usually gives a combined picture of increased intracranial pressure and primary optic atrophy with defects in the visual field. The tumors arising from the embryonic hypophyseal duct are practically the only lesions giving this combined picture. Rarely a suprasellar endothelioma may simulate the tumors of the duct, but here primary optic atrophy is generally found in one eye and choked disk in the other, probably because an endothelioma rarely occurs exactly in the midline.

The condition shown by the roentgenogram varies with the seat of the adamantinoma. When the tumor develops in apposition to the anterior hypophyseal lobe, relatively early enlargement of the sella turcica is to be expected. This may appear at first as a simple increase in size, with thinning of the sellar floor, or the anterior or posterior clinoid processes may show erosion. Actual loss of the clinoid shadows is usually noted by the time the tumor is large enough to give symptoms.

A tumor arising at the upper end of the infundibulum may show a normal sella, even when the growth has reached considerable proportions. It may, on the other hand, give a picture characteristic of a primary intrasellar tumor. This would suggest a downward prolongation of the growth into the sella, a condition which was found in one of the cases reported here. Upward growth with impingement on the third ventricle and resulting hydrocephalus may show in the roentgenogram the characteristic cranial deformities of this condition. Separation of the sutures or the presence of so-called digital markings may be noted, all indicative of increased intracranial pressure.

The most characteristic roentgen-ray observation is a suprasellar shadow. Calcification here is practically always in the wall of a cyst or of an adamantinoma, and roentgen-ray evidence is sufficient to make a diagnosis. The shadow is often crescentic in outline, suggesting the wall of the tumor. Suprasellar calcifications have been noted in a large number of adamantinomas. It was present in case 2, which is to be described later.

The presence of the tumor at operation is suggestive, but a definite diagnosis cannot be made except by microscopic examination. In the three cases in which I operated, the wall was quite firm, and definite calcification was noted in two. In the first case, a cyst containing straw-colored fluid was found. In the walls of this cyst was a dense layer of white or slightly cream-colored granular material, which was friable and appeared quite dry. The second patient presented a solid mass of similar nature, closely resembling dried sebaceous material, but on the whole considerably whiter. The third patient had a large cyst containing brownish-yellow, almost syrupy fluid, rich in cholesterin crystals. The right wall and the floor of the cyst were covered with calcareous masses, some of which resembled mother of pearl. The noncalcareous portions of the tumor were brownish yellow in contradistinction to the almost white appearance of the tumor in the first two cases.

The histologic structure varies in different parts of the same tumor, but according to Critchley and Ironside, "the presence of a single row of columnar cells, corresponding in structure to the embryonic ameloblasts, and arranged in a palisade formation at the periphery of the epithelial masses, is the criterion for diagnosing the tumor as an adamantinoma."

Ewing [7] states:

> While commonly well encapsulated there may be invasion of surrounding soft tissues and bone. The main structural type is that of adenoid cystic epithelioma. In a cellular connective tissue stroma lie anastomosing masses of epithelium, the outer layers of which are cylindrical, while the inner layers become flattened and vacuolated. There is often a distinct tendency to reproduce the reticulated structure of adamantinoma, and many small cysts form in the liquefied central areas, as well as in the edematous stroma. Or squamous metaplasia is pronounced, pearls and intercellular bridges form, and keratohyaline granules appear. In some cases squamous cells are wanting, and the tumor is composed of many closely packed papillae, lined chiefly by cylindrical cells (Lewis). Either in the epithelial masses or in the walls of vessels calcific concretions may form.

Bailey [8] settled the much disputed question regarding the presence of keratin and keratohyalin. In absolutely fresh material from three cases

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7. Ewing, James: Neoplastic Diseases, Philadelphia, W. B. Saunders Company, 1922, p. 938.

8. Bailey, Percival: Note concerning Keratin and Keratohyalin in Tumors of the Hypophysial Duct, Ann. Surg. **74**:501 (Oct.) 1921.

he was able to demonstrate keratinized cells in two and granules of keratohyalin in all three. Two of the patients had cysts containing cholesterin crystals.

The marked adiposity frequently associated with pituitary and hypophyseal duct tumors has attracted considerable clinical attention, but Warthin [9] appears to have made the only pathologic study of the nature of these fatty deposits. He based his contribution on two cases of dyspituitarism with adiposity, in one of which the tumor was an adamantinoma. He investigated particularly the nature of the lipin contents of the liver and described a hitherto unknown type of hepatic necrosis. His conclusions are of sufficient importance to be quoted in full. He states:

> In hypopituitarism there is a peculiar obesity due to infiltration of various cells of the body with a mixture of lipins:—glycerin-esters and cholesterol-esters. This condition of cholesterol liposis is especially marked in the liver and adrenals, but is scattered all over the body. With deficiency of hypophysis function there appears to be associated a cholesterol retention or infiltration. Hypopituitarism must, therefore, be classed among the xanthelasmic conditions, and is related in kind to diabetic liposis and Gaucher's disease.
>
> The hypophysis is either directly or indirectly concerned with lipin metabolism, particularly with cholesterol steatosis. Postmortem hyperpyrexia may be associated with hypopituitarism and the obesity resulting from the latter condition.
>
> In the livers of two cases of hypopituitarism there occurred a peculiar intraperipheral zonal necrosis, unlike all previously described forms of zonal liver necrosis. Associated with this necrosis is a reparative fibroblastic proliferation, giving rise to the picture of an early intralobular cirrhosis. The relationship of this hepatic change to the hypophysis conditions remains to be shown.

It is interesting that the three cases of pituitary adamantinoma forming the basis of this report represent the two types of practically all the pathologic changes which have been noted in these cases.

The two types of endocrine disturbance are presented. The first patient was thinner than normal and would be placed in the infantile or Lorain group. The second, belonging to the Fröhlich group, showed marked adiposity, especially over the hips and about the waist, and was of the type studied by Warthin. The third case did not show evidence of hypophysial dysfunction. None of my patients were excessively drowsy at the time of admission, although this seems to have been a common sympton in the cases previously reported.

The two main locations for the development of adamantinoma are represented in these patients. The patient in case 1 had an intrasellar tumor, evidently developing from the extreme lower end of the infundibular stalk. The patient in case 3 showed a similar lesion. In

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9. Warthin, Aldred Scott: A Study of the Lipin Content of the Liver in Two Cases of Dyspituitarism, J. Lab. & Clin. Med. **2**:73 (Nov.) 1916.

case 2 the patient presented a suprasellar tumor, apparently arising from the upper end of the infundibulum. The roentgen-ray evidence likewise represented the two types previously mentioned, case 1 showing enlargement of the sella turcica with destruction of the posterior clinoid processes, while cases 2 and 3 showed suprasellar calcification.

The changes in the eye also represented the two types of pathologic change in the fundus encountered in these tumors; in cases 1 and 3 primary optic atrophy was present; in case 2, choked disks.

Figure 1

Figure 2

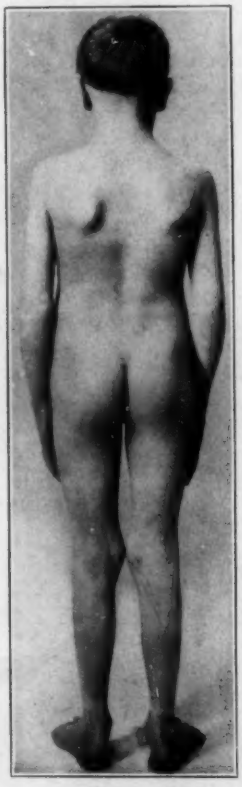

Figure 3

Fig. 1 (case 1).—Normal stature; legs and arms are thin. This photograph, taken after operation, shows the absence of visible scars.

Fig. 2 (case 1).—General build normal for a boy aged 9 years. The arms appear rather long.

Fig. 3 (case 1).—Prominent scapulae and thin legs suggest the Lorain type of hypopituitarism.

REPORT OF CASES

CASE 1.—*History.*—V. W., a boy, aged 9, was admitted to the University Hospital on Nov. 2, 1925, complaining of failing vision. His family history and previous personal history were normal.

Nearly a year before coming to the hospital, he had made grimaces and said there seemed to be something in his eyes. Actual visual disturbance was not apparent, however, until about five months before. At that time it was noticed that when picking strawberries he picked both the green and the red, although he did not have trouble in actually seeing the berries. This loss of color perception was not understood at first, and the boy was considered careless, until it was found by actual test that he could no longer distinguish between the two colors. With the starting of school, two months before the boy came to the hospital, actual diminution of vision was noted, and soon he was unable to read. He had not had headache, dizziness or nausea and had not vomited. The output of urine apparently had been normal.

Physical Examination.—Examination showed a well proportioned boy of good stature for his age (fig. 1). He was somewhat thinner than normal, but was not actually emaciated (figs. 2 and 3). The head was of normal size and shape. Extra-ocular movements were normal. The pupils did not react to light, but there was slight contraction for accommodation. There was some nystagmus on

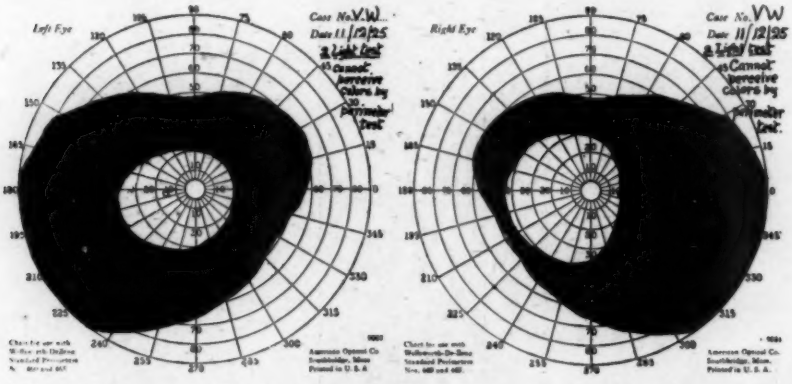

Fig. 4 (case 1).—Visual fields before operation, determined by two-light tests, as vision was so reduced the regular perimeter examination could not be made. Color perception was entirely lost.

looking laterally. Tension was normal. The optic disks were pale, with a slight blurring on the right and apparent slight swelling on the left, the swelling being confined to the disk itself. The ophthalmologic report showed consecutive optic atrophy with almost complete temporal hemianopsia on the right and marked contraction of the visual field on the left. Color perception was entirely lost. The vision was so poor that examination could be made only by the two-light test (fig. 4). Results of the neurologic examination, except for the changes in the eye, were negative. A roentgenogram of the skull showed a definite increase in the depth and width of the sella turcica with a thinning of its floor and destruction of the posterior clinoid processes. There were definite digital markings indicative of increased intracranial pressure (fig. 5). Results of examinations of the urine and of the blood were essentially negative. A diagnosis of pituitary tumor was made, and operation was recommended.

Operation.—Operation was performed on Nov. 13, 1925. A large osteoplastic flap was turned downward in the right frontoparietal region. The dura was found to be under practically normal tension. The frontal lobe was elevated, and the pituitary region was approached from the frontal lateral direction.

When the region of the sella turcica was exposed, both optic nerves were found elevated and pushed laterally to either side by a tumor bulging up from the sella turcica in front of the chiasm and between the optic nerves (fig. 6). This tumor was solid, except for a central area between the optic nerves, which was definitely cystic. Aspiration of this yielded a deep yellowish fluid. About 1.5 cc. was obtained. The capsule of the tumor was then incised, and its contents were removed by a sharp curet and pituitary forceps. A considerable amount of the capsule was removed, but a portion of it on either side was firmly adherent to the carotid arteries, and this portion could not be excised. The inside of the remaining portion of the capsule was painted with Zenker's solution. The optic

Fig. 5 (case 1).—Enlargement of the sella turcica and almost complete destruction of the posterior clinoid processes.

nerves dropped down to their normal position. The pathologic report showed an adamantinoma, the complete description of which follows:

Pathologic Diagnosis.—The diagnosis was adamantinoma, a tumor of the craniopharyngeal duct. Pituitary gland tissue was not present in the material. Microscopically, the tumor consisted of irregularly branching cords and masses of epithelial cells of the squamous cell type showing pronounced intercellular bridges and peripheral palisade arrangement. The stroma was a dense, finely fibrillated, nearly hyaline connective tissue with spindle or stellate nuclei resembling that of a tooth-bud formation. In the central portion of the larger cell masses there was a hyaline transformation of the epithelial cells into a hard, irregularly-fragmenting substance resembling an atypical enamel. In a few

areas lime-salts had been deposited in this. The fracture was irregularly conchoidal. The blood supply was fairly abundant, in the form of irregular sinusoidal spaces and dilated capillaries in the youngest stroma. The neoplasm was precisely like the adamantinomas of the jaw and was interpreted as a pituitary adamantinoma originating in the craniopharyngeal duct, slowly replacing the sella turcica and pituitary gland by pressure atrophy and exerting pressure

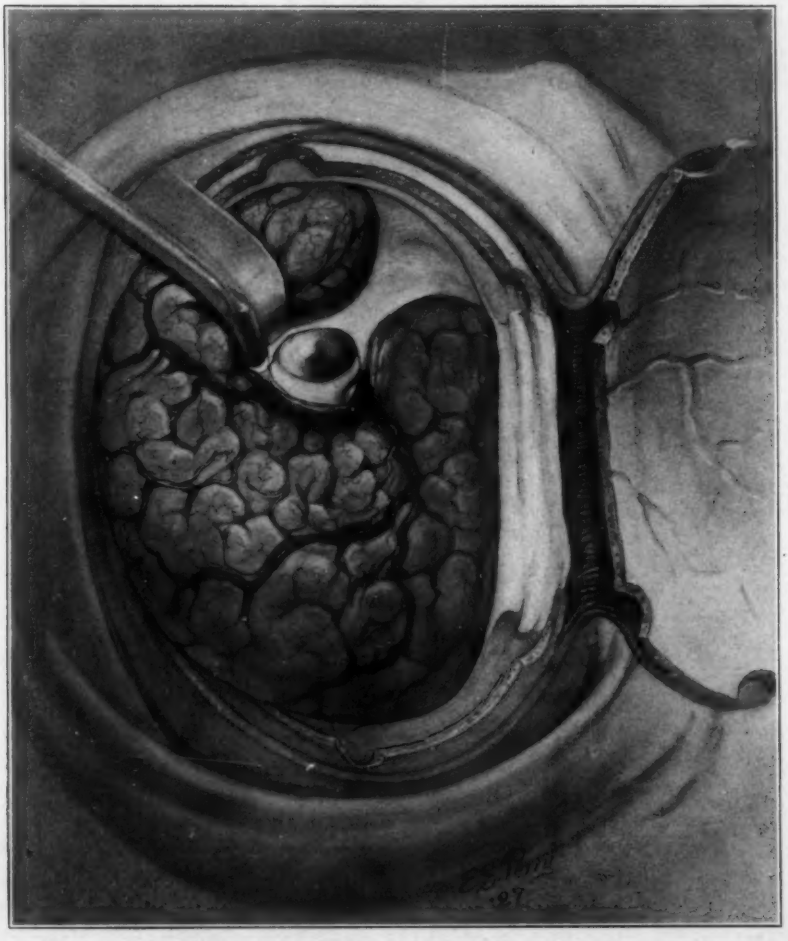

Fig. 6 (case 1).—Intrasellar adamantinoma with central cyst. There is marked pressure on the optic nerves and chiasm.

on the optic chiasm. Its malignancy was only of local growth and pressure; there was no danger of metastasis.—A. S. Warthin (figs. 7, 8, 9).

Convalescence and Recovery.—Convalescence was satisfactory. The patient's visual acuity was greatly improved, and within a week after operation he could see a fine thread. Roughly tested, there was a slight early improvement in the visual fields. Reexamination on Feb. 24, 1926, showed a progression of the optic atrophy in the left eye, so that on that date there was no color perception.

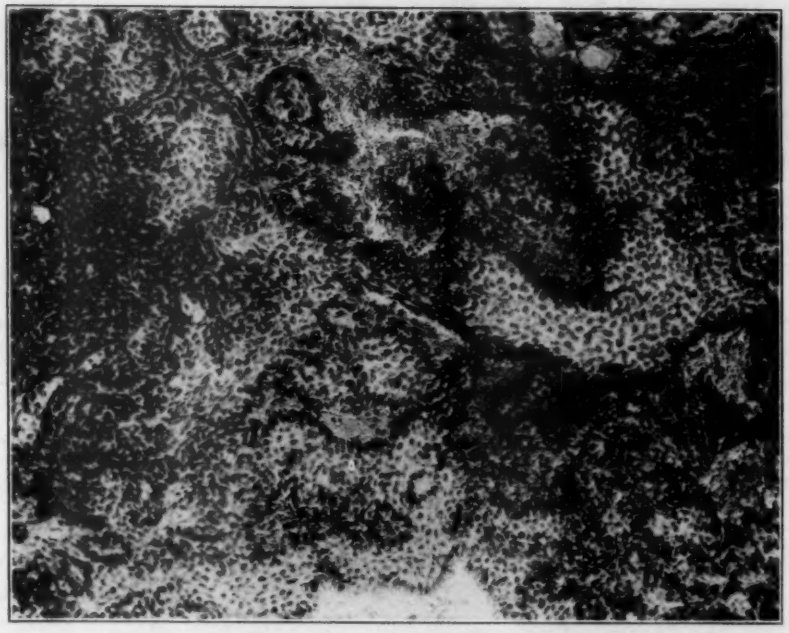

Fig. 7 (case 1).—Adamantinoma of the craniopharyngeal duct. Solid masses of prickle cell epithelium with peripheral palisade arrangement. No hyaline change is present in this area except at the lower part of the section.

Fig. 8 (case 1).—Adamantinoma of the craniopharyngeal duct. Hyaline degeneration (atypical enamel formation) of epithelial masses. Palisade arrangement of the basal layer of epithelial masses, producing a pseudo gland-like appearance.

The right eye showed marked improvement in the form fields, and blue and red were now recognizable in a small segment on the nasal side (fig. 10). He continued to develop normally after the operation. In January, 1927, it was reported that he was showing signs of diabetes insipidus and desired to drink large quantities of water and passed a correspondingly increased amount. We recommended daily injections of pituitary extract. His physician reported that he tried 0.5 cc. a day hypodermically and later increased the dose to 1 cc., but apparently it did not cause any diminution in the urinary output. A later report giving actual measured intake and output showed that this was not excessive for a boy of his age. Whether he had had a temporary diabetes insipidus is questionable, but at the time of the final report there was no evidence of it.

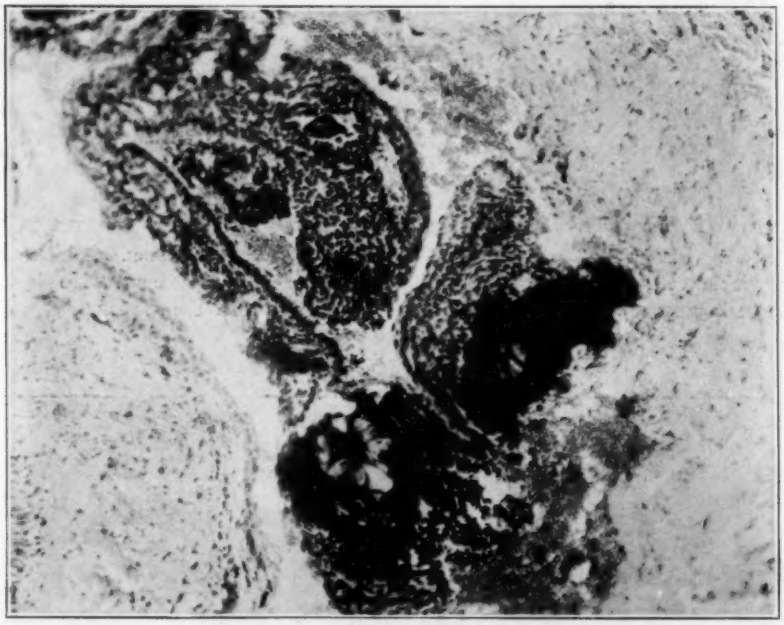

Fig. 9 (case 1).—Calcification of atypical enamel masses formed by prickle cell epithelium; adamantinoma of the craniopharyngeal duct.

Case 2.—*History.*—M. M., a girl, aged 10, was admitted to the University Hospital on Nov. 17, 1926, because of rapidly failing vision. Her previous history was essentially negative. She had walked and talked at the age of 1 year. Her mental and physical growth had proceeded normally, except for the development of excessive adiposity. The present illness had started one year before, with severe headaches, nausea and vomiting when she awoke in the morning. She was usually relieved by noon. Headaches and vomiting continued at intervals of about ten days until six weeks before admission, since which time she had remained free from these symptoms. Appendectomy had been performed in the hope of relieving the nausea and vomiting, but without benefit. Her vision was tested in January, 1926, and glasses were prescribed. No lesion of the fundus was noted. For some time she had noticed that her vision was failing, and her parents had noticed a rapid loss of vision during the two weeks preceding admission. The patient said that her vision had been poor

and steadily failing for some weeks, but she did not tell her parents, as she did not wish to worry them. Recently the loss of vision had been rapid, as evidenced by her ability on admission to count fingers held before her at a distance of three feet, but four days later she could no longer count fingers even when they were held close to her face. Her appetite and intake of water had not been unusual.

Physical and Neurologic Examinations.—The patient was generally obese, with excessive deposits of fat above the hips and around the waist (figs. 11 and 12). The head was of normal contour. The cranial nerves, with the exception of the optic, were normal. The neck, thorax, abdomen and extremities were normal. All reflexes were present and equal. There was no disturbance in sensation. Examination of the fundus showed a rather marked optic atrophy with papilledema in both eyes. In the right eye, the choked disk measured 3 diopters; in the left, from 4 to 5 diopters. The pupils reacted to light and in accommodation. The visual fields showed complete loss of color perception in both eyes. On the left, a small area for white was preserved in the temporal field; on the right, only a small area in the central nasal field was present (fig. 13).

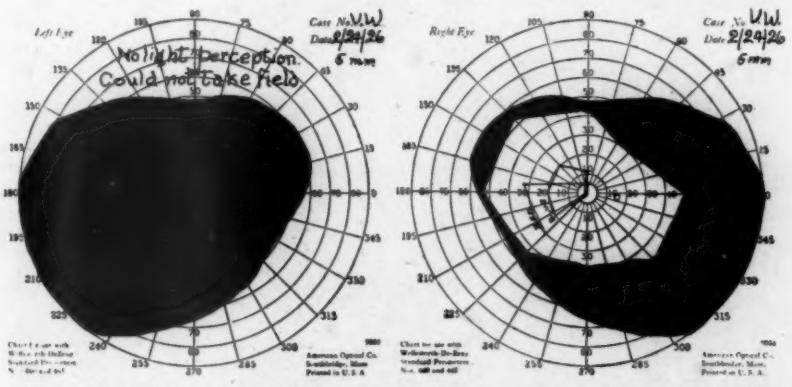

Fig. 10 (case 1).—Visual fields taken two months after operation. There is marked improvement in the form field in the right eye, examination being made with the standard perimeter. Color perception for blue and red has returned in a small area in the right nasal field. In the left eye the optic atrophy present before operation has progressed to complete atrophy with loss of light perception.

Basal metabolism tests showed minus 15 per cent (Du Bois standard); minus 16 per cent (Talbot standard), with a pulse rate of 84. Glucose tolerance: fasting, 0.095; one-half hour after taking 1.7 Gm. of glucose per kilogram of body weight, 0.174; one and one-half hour period, 0.094; two and one-half hour period, 0.094. Results of examination of the urine were negative. Examination of the blood revealed: hemoglobin, 82 per cent; red corpuscles, 3,520,000; white corpuscles, 7,600. Differential blood count: polymorphonuclears, 34 per cent; lymphocytes, 61 per cent; basophils, 0 per cent; eosinophils, 3.5 per cent; transitional cells, 2.5 per cent.

The roentgenogram of the head showed definite digital markings indicative of prolonged intracranial pressure. The sella was only slightly enlarged, but the anterior clinoid processes were much thinner than normal, and the posterior clinoid processes were apparently completely destroyed. Above the sella was an irregularly calcified mass, roughly circular in outline and suggesting calcification in the wall of a suprasellar cyst (fig. 14).

The diagnosis made was suprasellar cyst, evidently pressing upward on the third ventricle, thereby interfering with the flow of cerebrospinal fluid with resulting choked disks and probably beginning hydrocephalus. It also pressed downward, possibly causing a primary optic atrophy and symptoms of hypopituitarism, as evidenced by the excessive adiposity, the low basal rate and the increased sugar tolerance. Operation with an approach to the tumor from above the sella offered the only means of relief.

Operation.—Operation was performed on Nov. 22, 1926. A large osteoplastic flap was turned downward from the right frontoparietal region. The dura was

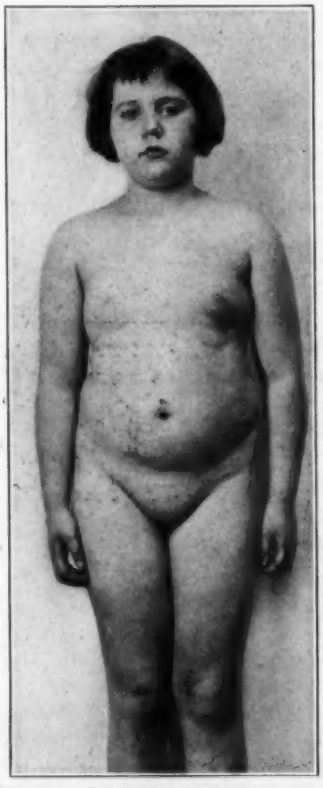

Figure 11

Figure 12

Fig. 11 (case 2).—Marked adiposity, especially above the hips and around the waist. Apparent mammary development is due entirely to fat.

Fig. 12 (case 2).—The excessive deposits of fat above the hips and around the waist are well shown.

under considerable tension. This was relieved by tapping the dilated right lateral ventricle with the evacuation of a large amount of clear cerebrospinal fluid. The dura was opened widely, the base of the flap being placed near the midline. In spite of the complete relief of pressure afforded by evacuation of the ventricle, it was difficult to elevate the median inferior surface of the frontal lobe. This was due to the fact that the tumor extended well up into the third ventricle. The right and left optic nerves and the chiasm were, however,

exposed without difficulty. There was no tumor in the anterior portion of the sella turcica, but one could see the diaphragm of the sella pushed sharply downward. The diaphragm was thin, and the pituitary, as viewed through the diaphragm, appeared normal. The brain was elevated posterior to the chiasm, which later had been pushed downward and forward by the tumor occupying the region of the floor of the third ventricle. This tumor extended downward posterior to the posterior clinoid process, thus passing in front of the pons, and a tongue also passed anteriorly into the posterior part of the sella, elevating the posterior edge of the chiasm and pushing the whole chiasm sharply forward and downward. The capsule of the tumor was opened posterior to the chiasm, and a slightly calcified wall was found. Within the wall of this cyst a dry, whitish, sebaceous-appearing material was packed tightly. Hair was not present. The dry, rather hard tumor mass was removed with a curet. Much of the capsule of the tumor immediately posterior to the chiasm and that portion passing into the sella was removed. Some of the capsule was rather firmly adherent to the under side of the optic tracts and of the chiasm. When an attempt was

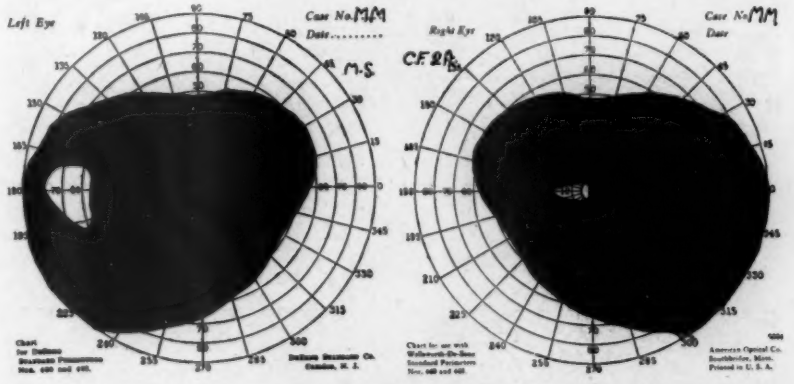

Fig. 13 (case 2).—Visual fields; color perception was entirely lost. There is complete right homonymous hemianopsia and extreme contraction of form fields on the left. Fingers could be counted at a distance of two feet.

made to remove the capsule posterior to the posterior clinoid process, the patient suddenly became pulseless, and it was necessary to cease further attempts to remove the tumor; how much remained in the region of the third ventricle was not determined. The dura was closed, the osteoplastic flap returned to position, and the scalp closed in layers.

A transfusion of blood was given immediately, and the pulse showed marked improvement, but the patient died about three hours later. Autopsy was refused.

The exact cause of the sudden collapse was not clear. Up to the minute the pulse became imperceptible it had been of good quality, with a rate of 126 and a blood pressure of from 108 to 100 systolic and from 78 to 76 diastolic. Appreciable bleeding did not occur at any time. The operation confirmed the preoperative conception, the tumor having pushed upward the floor of the third ventricle with resulting hydrocephalus. It had also pressed the optic chiasm forward and downward. The tumor, however, proved to be solid rather than cystic.

Pathologic Diagnosis.—A tumor of the craniopharyngeal duct of the type of an adamantinocarcinoma was found. In part, it was infiltrating an atypical

Fig. 14 (case 2).—The sella turcica is somewhat enlarged and the posterior clinoid processes are practically destroyed. Above the sella can be seen a calcified mass in the wall of the adamantinoma. Digital markings, indicative of increased intracranial pressure, are present.

Fig. 15 (case 2).—Tooth-bud-like growth of prickle cell epithelium with palisade peripheral arrangement; adamantinocarcinoma of the craniopharyngeal duct.

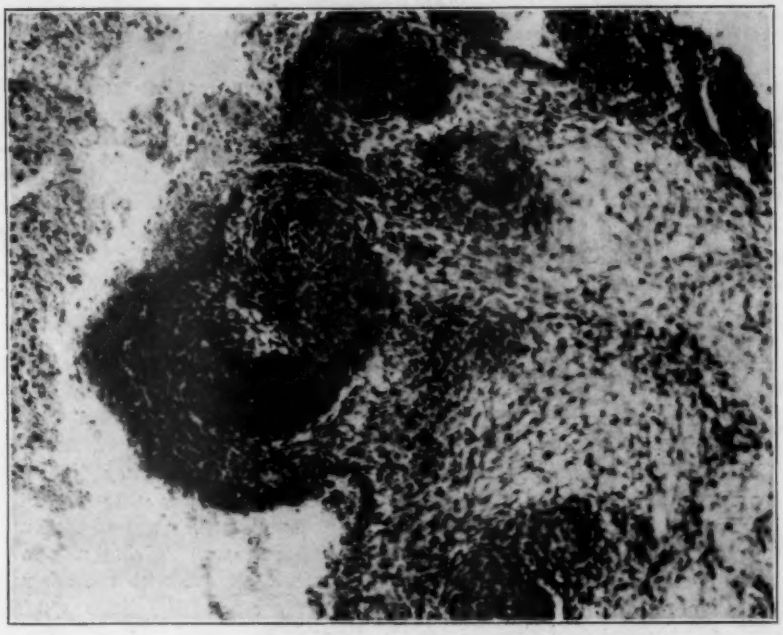

Fig. 16 (case 2).—Adamantinocarcinoma of the craniopharyngeal duct. Tooth-bud-like epithelium formations infiltrating the brain. Higher magnification of conditions shown in figure 15.

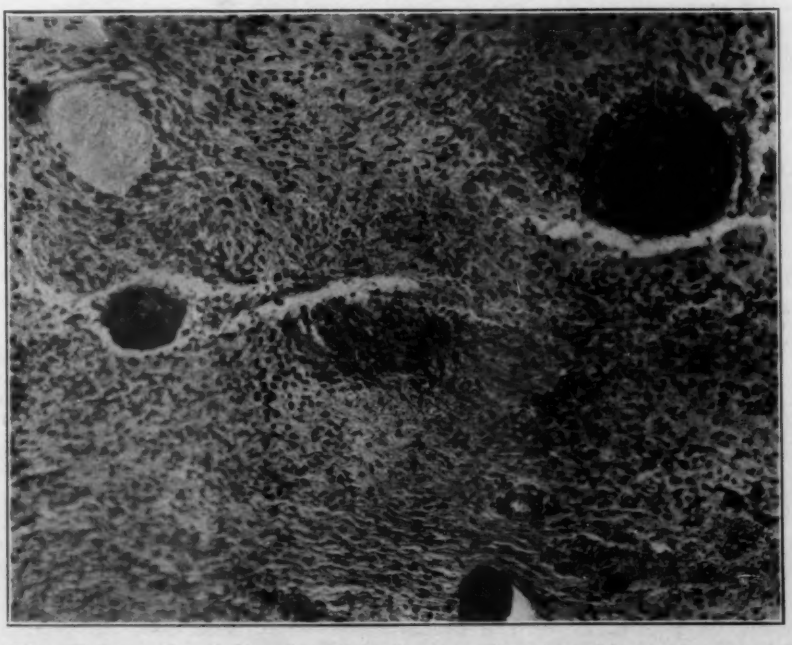

Fig. 17 (case 2).—Infiltration of brain tissue by adamantinocarcinoma of the craniopharyngeal duct. In the upper part on the left is a cord of tumor cells showing enamel transformation of prickle cell epithelium; at the bottom is a calcified cord. Four different stages of growth of a tumor are represented in the photomicrograph.

neuroglia. Throughout the growth there were numerous pink-staining hyaline masses, probably representing an atypical enamel formation, and many of these were calcified.—C. V. Weller.

Pathologic Description.—The microscopic appearances of this tumor were identical with those of the growth in case 1, with the exception that this one showed a greater degree of differentiation and some degree of infiltration into the adjacent brain tissue and meninges. It consisted of cords and masses of prickle cell squamous epithelium showing peripheral palisade arrangement, a dentine-like stroma and a central peculiar hyaline transformation of the epithelial cells into conchoidally-fragmenting dense hyaline material showing a strong affinity for lime salts, leading to the production of irregularly nodular, extremely hard concretions. These appearances were interpreted as representing an atypical enamel formation. The structure of the tumor was identical with that of the adamantinomas of the jaw; it represented a more advanced stage than that in case 1 and exhibited a greater degree of local malignancy (infiltration and pressure atrophy). Its malignancy was local only, and metastases were not to be expected. It was interpreted as a developmental disturbance of the craniopharyngeal duct, representing abortive tooth-bud formation, giving rise to cell masses of enamel-organ type, and it was, therefore, classed with the adamantinomas. No remains of the pituitary gland were present. Fröhlich's syndrome would probably have developed.—(A. S. Warthin.)

Case 3.—*History.*—R. B., a girl, aged 6, was admitted to the University Hospital, Sept. 8, 1927, complaining of headaches and failing vision. The past history was unimportant. She began to talk and walk at 1 year of age. The body and mental growth had been regular and normal. She had not had any contagious diseases. The family history was negative for any endocrine disturbances.

In August, 1926, she developed marked conjunctivitis with profuse lacrimation, which her physician diagnosed as "hay-fever." However, she was drowsy, and for three days could be aroused for only a minute or so at a time. These symptoms disappeared in about two weeks, following which she was free from symptoms until the first of February, 1927. She then developed a severe headache and in two or three hours vomited profusely. The headache, which was referred to the left posterior parietal region, persisted, however, and seemed to increase in severity. The tonsils were removed the last of February in the hopes of controlling the headache, but without relief. She again became drowsy. She complained of pain in the eyes, especially in the presence of a bright light. Headaches in the left posterior parietal region continued for three months, during which time she was confined to bed. She was then free from symptoms and was as active as any normal child until August, 1927, when the headache reappeared, but in the right posterior parietal region. The pain was not constant as before, occurring only two or three times a day. She usually awakened in the morning crying from the headache. Sometimes the pain lasted for only a few minutes, and generally disappeared suddenly. She lost her appetite and complained, "I have a nasty taste in my mouth." At one time she likened this taste to that of rotten eggs. Her eyes were then examined for possible cause of the headache. Optic atrophy was found in the left eye, and glasses were prescribed. The headaches persisted, and a month later she entered the University Hospital. There had not been any nausea or vomiting since the attack in February. The weight had remained normal and polydypsia or polyuria had not been noted.

Physical Examination.—The patient was well developed and normally proportioned for her age (fig. 18). She was not adipose and did not have any abnormal local deposits of fat. The head was of normal size and configuration (figs. 19 and 20). The cracked-pot sound was not present. Movements of the eyes were normal in all directions. The pupils were equal and contracted to light and in accommodation. Ophthalmoscopic examination showed primary optic atrophy involving the entire left disk and beginning in the nasal half of the right disk. Perception of light was present only in the left eye. The form field in the right eye was confined to the nasal half. Vision in this area was apparently normal.

Figure 18

Figure 19

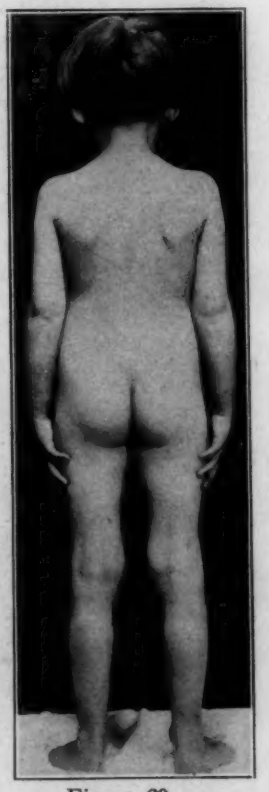

Figure 20

Fig. 18 (case 3).—Normal configuration in a child of 6. There is neither thinness as in case 1 nor adiposity as in case 2. The head is of normal shape and size.

Fig. 19 (case 3).—Normal development of body. The protuberant abdomen is not due to fat but to poor posture.

Fig. 20 (case 3).—No evidence of hypopituitarism in contrast to cases 1 and 2. The skin is soft and of fine texture. The hair of the head is abundant.

The neurologic examination was normal. Physical examination of the thorax, abdomen and extremities did not disclose any abnormalities. The child was alert and apparently normal mentally.

Roentgen-ray examination showed an enlargement of the sella tursica with some destruction of the posterior clinoid processes. A calcified shadow was

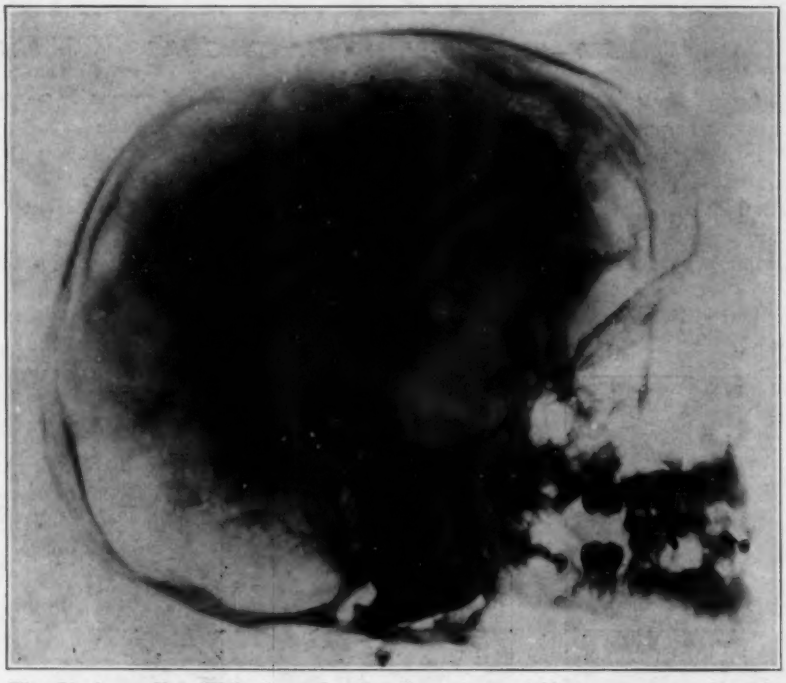

Fig. 21 (case 3).—Thinning of sellar floor and calcified mass extending from sella upward and backward.

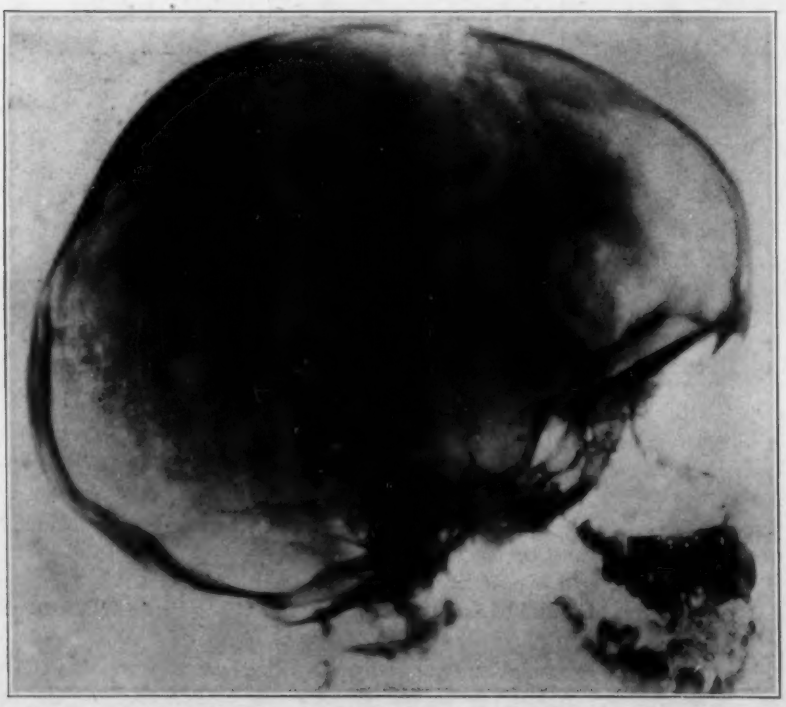

Fig. 22 (case 3).—This illustration is taken at a different angle from that in figure 21 and shows the calcified mass apparently more posteriorly. It shows clearly the enlargement of the sella turcica and the partial destruction of the posterior clinoid processes.

seen extending from within the sella turcica upward about 1.5 cm. on the right (figs. 21, 22 and 23).

Determinations of basal metabolism were satisfactory and were recorded as plus 9 per cent, with a pulse rate of 80 on the first examination; they were recorded as plus 6 per cent with a pulse rate of 90 on the second examination.

The glucose tolerance test showed: fasting, 71 mg. per hundred cubic centimeters; one hour period, 93 mg.; two hour period, 88 mg.; three hour period, 75 mg.

Examinations of the blood and urine were normal.

A diagnosis of a calcified tumor in the sella and suprasellar regions, probably a pituitary adamantinoma, was made and operation advised.

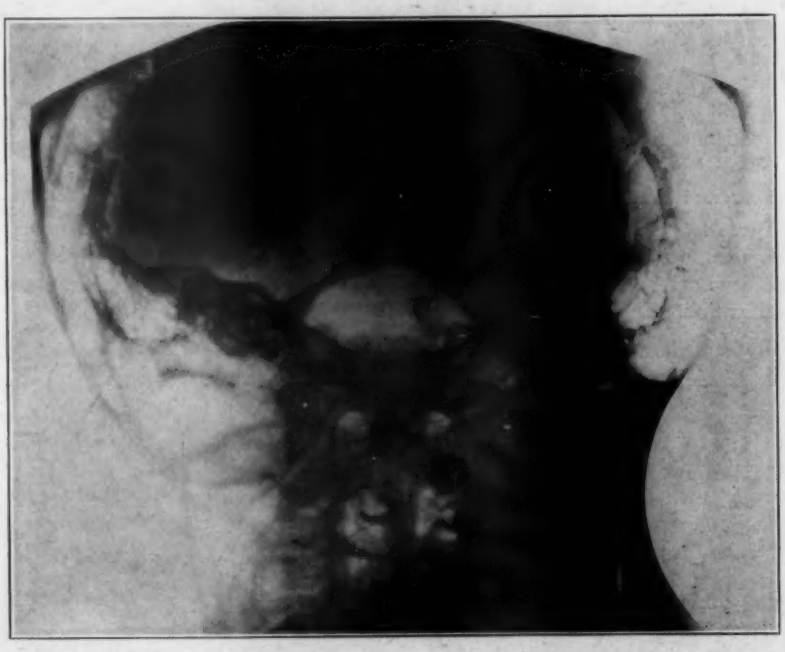

Fig. 23 (case 3).—Anteroposterior view of the widely separated anterior clinoid processes and the calcification in the right wall of the cyst.

Operation.—Operation was performed on Sept. 13, 1927. A large osteoplastic flap was reflected from the right frontoparietal region. The dura was under normal tension. The frontal lobe was elevated, exposing the region of the sella turcica. A large, smooth, encapsulated tumor was found arising within the sella turcica and presenting in front of the optic chiasm. The right and left optic nerves were pushed upward and outward. The right third of the tumor appeared solid and was pinkish. The left two thirds appeared definitely cystic and was bluish white. The cyst was aspirated and about 10 cc. of brownish-yellow, almost syrupy fluid, rich in cholesterin, was obtained. The capsule of the tumor was incised, and the solid portion at the right was found to be a much thickened wall of the cyst. Adherent to its right lateral wall were masses of yellowish-white concretions. One discrete mass measured 1.5 by 1 by 1 cm.

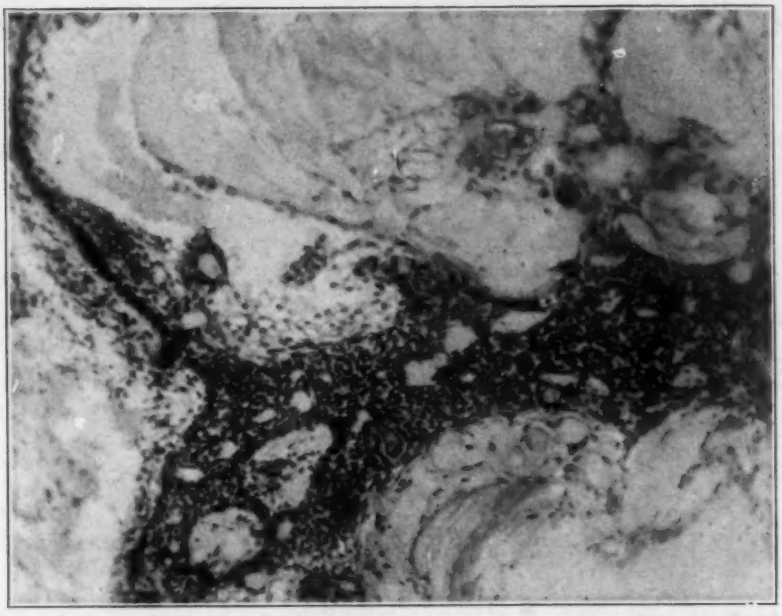

Fig. 24 (case 3).—Area showing structure of adamantinoma. Appearance of squamous epithelium with intercellular bridges, slight palisade arrangement and large masses of laminated, dense epithelial hyaline transformation, showing calcification. Atypical enamel formation.

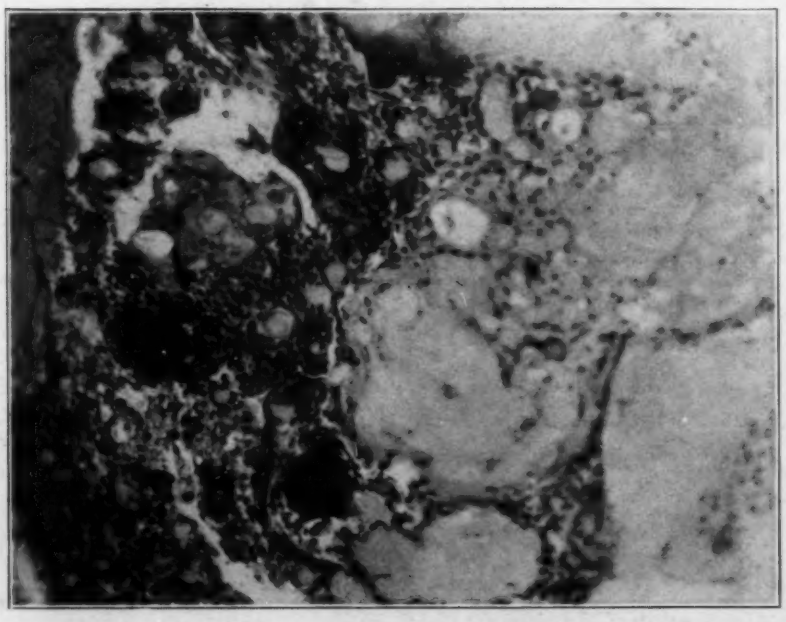

Fig. 25 (case 3).—High power appearance of figure 24, showing the epithelial hyaline transformation of squamous cell epithelium with intercellular bridges. Formation of atypical enamel from epithelium. The palisade arrangement does not show in this field.

Fig. 26 (case 3).—High power appearance of atypical enamel formation, showing laminated structure and conchoidal cleavage. Lime salt deposits in enamel masses are shown.

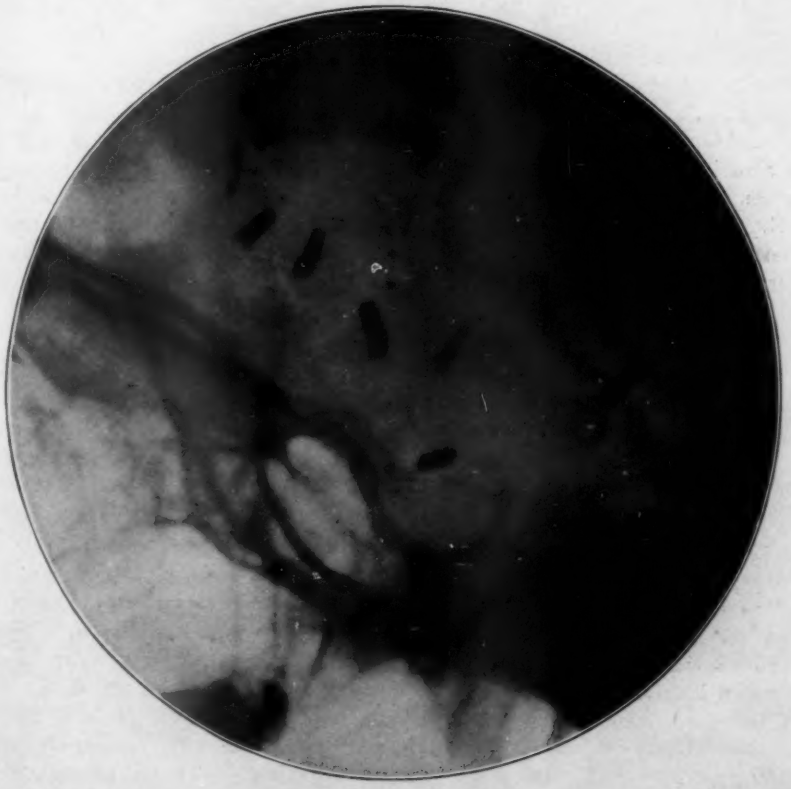

Fig. 27 (case 3).—Postoperative appearance, showing abscence of calcification in sella and suprasellar region. The silver clips placed on the dura are considerably magnified, since they are on the side of the head opposite the film.

Similar masses of solid material containing concretions, some of which resembled pearl, covered the floor of the cyst. After its contents were evacuated, the entire cyst wall was removed. Due to the elevation of the chiasm and the partial destruction of the posterior clinoid processes, it was possible to see the anterior surface of the pons and the basilar artery. Both optic nerves had been markedly stretched by the tumor: the right was uniformly thinned; the left, while much flattened throughout its course, appeared nearly divided just distal to the chiasm. Neither nerve was injured during the operation. A small, flattened plaque, apparently the remains of the pituitary gland, remained on the floor of the sella turcica. The dura was sutured, the osteoplastic flap returned to position and the incision closed in layers. The child's condition at the completion of the operation was excellent.

Pathologic Diagnosis (C. S. Warthin).—The condition was diagnosed as a typical adamantinoma of the craniopharyngeal duct and a cyst in a Rathke's pouch with cholesteatoma. The cyst was lined in part by squamous epithelium, in part by columnary epithelium. Some of the squamous epithelium showed intercellular bridges. This is a more complex disturbance of the craniopharyngeal duct, as it contains areas of different tissues.

Pathologic Description (C. V. Weller).—The material removed presented varying appearances in different portions. Certain areas, apparently capsular portions of the mass, showed a dense connective tissue through which were scattered cords and small masses of epithelial cells which showed a distinct peripheral palisade arrangement. Small cystic structures were also present, some of which showed a squamous epithelial lining. In other areas there were dense granular and coarsely laminated or pseudoprismatic masses staining pink with eosin, except in those areas in which they were partially infiltrated by lime salts. Many of these masses had a distinct conchoidal fracture and were found in association with prickle celled epithelium in a matrix of looser, somewhat myxomatous connective tissue. Areas of secondary degeneration and old hemorrhage were represented by deposits of cholesterin and much phagocytized blood pigment. The structure was therefore that of a disturbance of development of the craniopharyngeal duct with typical areas of adamantinoma and much formation of enamel.

Convalescence and Recovery.—Convalesence was rapid and without incident. Within twenty-four hours after the operation the child was able to count fingers with the left eye, although previously only perception of light was present. This return was confined to the central vision. The nasal field on the right remained normal; the temporal field seemed slightly increased. A roentgenogram of the sella turcica showed that all the calcareous material had been removed (fig. 27).

The child returned to the hospital for examination one month after the operation. The general condition was excellent. Vision in the left eye was still confined to the central field, but there was definite improvement in the right. The nasal vision remained normal, and about 30 degrees of temporal vision had been regained. While at home she had shown moderate polydypsia and polyuria, but this was growing less. Measurements of intake and output had not been made, but a frequency had been noted in her desire to drink and to urinate. When she was examined, it was found that this tendency was so slight that the administration of pituitary was not considered necessary.

SUMMARY

Three cases of adamantinomas in the pituitary region are reported. The first patient was possibly thinner than normal and might be placed in the Lorain group. The second presented a typical Fröhlich syndrome of excessive adiposity and low rate of basal metabolism. The third belonged in the rare group having an intrasellar adamantinoma with normal basal metabolism and sugar tolerance and without any physical evidence of dyspituitarism. The two tumors illustrate two of the locations in which adamantinomas may develop in the primary region. The first and third cases were primarily intrasellar, and the tumor undoubtedly arose in the extreme lower end of the infundibular stalk. In the second, the tumor arose from the extreme upper end of the infundibulum. In the first and third primary optic atrophy was present; in the second, choking of the optic disk with optic atrophy and definite hydrocephalus, due to blockage of the third ventricle.

A tentative diagnosis of a pituitary adamantinoma should be easily made, although the symptoms vary with the location and size of the tumor. The majority of patients present the Fröhlich syndrome of dystrophia adiposo-genitalis. In a child with this syndrome, with simple excessive adiposity, or a marked increase in weight, the possibility of a pituitary adamantinoma should immediately be suspected. A few patients, however, show unusual slenderness. Occasionally the physical development is normal.

Excessive drowsiness is a common symptom. Headache, nausea and vomiting may or may not be present, depending on the presence of increased intracranial pressure. Visual disturbances have been noted in every case, usually a slow, progressive loss with bitemporal or homonymous hemianopsia. The presence of primary optic atrophy or of papilledema depends on the location of the tumor.

The roentgen ray offers a valuable means of diagnosis. The sella turcica is usually enlarged, and the anterior and posterior clinoid processes are thinned or completely destroyed. In many cases calcification above the sella turcica is shown, and this definitely indicates the presence of a cyst or tumor. In many of these the lesion is undoubtedly a pituitary or hypophyseal duct adamantinoma.

Operation is always indicated, as no other treatment can give relief. While there is considerable difference of opinion as to the choice of operative procedures in true pituitary tumors, I believe that adamantinomas are best approached from above. Certainly when the tumor has originated above the sella turcica as in case 2, no other approach is feasible.

The prognosis is extremely grave, as a review of the literature indicates, although early operation may prolong life with adequate vision for an indefinite period. In a few cases it is undoubtedly possible to remove the tumor completely, as in case 3. The early diagnosis of a pituitary adamantinoma followed by early operation will materially increase this number and will at least conserve vision in those who cannot be cured.

POSTOPERATIVE MASSIVE ATELECTASIS *

I. THE INFLUENCE OF POSTURE

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The number of reported cases of massive atelectasis has been multiplied in the last few years. The spectacular clinical picture of the fully developed unilateral condition is now familiar. It occurs as a postoperative complication, following trauma, and associated with spontaneous painful diseases both intrathoracic and outside the chest. The importance of the atelectatic process in other types of postoperative pulmonary complications and in the bilateral form has not been clearly elucidated, but judging from the meager data available along these lines, it appears to be great. An explanation of the origin of postoperative massive atelectasis, therefore, will undoubtedly do far more than solve this clinical mystery, since it may prove to be a most important step in reducing the incidence of those fatal postoperative pulmonary complications now classified as pneumonia.

In spite of careful investigation, the original cause of postoperative massive atelectasis has not been proved. The discussion of its etiology is still in the realm of hypothesis, and in this paper we do not hope to be able to establish its ultimate etiology. However, all new observations in regard to the mechanism of massive atelectasis are valuable, and it is our purpose to report such data.

Harrington [1] remarked, in reporting a case, that the postoperative posture of the patient has received scant consideration in the literature on massive atelectasis. Briscoe [2] is alone in attributing the chief rôle in the etiology of this complication to the recumbency of the patient. His point of view was based on the observation of relative deflation of the bases of both lungs as the result of "prolonged quiet breathing in the supine position in such people as do not use the abdominal muscles to

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* From the Department of Surgery of the University of Rochester, and the Department of Surgery of Western Reserve University and the Lakeside Hospital.

1. Harrington, S. W.: Relief of Postoperative Massive Collapse of the Lung by Bronchoscopic Aspiration, Ann. Surg. **85**:152 (Jan.) 1927.

2. Briscoe, J. C.: The Mechanism of Postoperative Massive Collapse of the Lung, Quart. J. Med. **13**:293 (April) 1920.

fix their chests." This can be dismissed as the explanation of postoperative massive atelectasis for two reasons: (*a*) Such conditions obtain in most laparotomies, while the incidence of massive atelectasis is about 1 per cent; and (*b*) it offers no basis for the most significant manifestation of the complication, viz., displacement of the mediastinum. Several writers mention the interference with respiration arising from recumbency as having a secondary influence on the development of the condition (Bradford,[3] Hirschboeck,[4] Eades [5]). In all these cases the flat recumbent posture alone is considered. The only reference to the possible significance of a unilateral position in the development of postoperative massive atelectasis is the allusion of Harrington.[1] Tidy [6] explained the contralateral collapse associated with nonpenetrating wounds of the opposite thoracic wall as being due to the patient's lying on the well side and thus splinting its respiratory movements. Webb, Forster and Gilbert [7] have shown that if a normal person lies continuously on one side, there is marked displacement of the mediastinum and opacity of the lung on the dependent side. Such an effect, however, quickly disappears when the person turns on his back and takes a deep breath. Consequently, this resembles the relative airlessness at the bases of the lungs described by Briscoe,[2] and is entirely dissimilar to the clinical manifestations of unilateral massive atelectasis.

THE INFLUENCE OF POSTURE

Our interest in the influence of posture in the development of massive atelectasis was awakened by the following unusual case:

CASE 1.—*History.*—J. M., a Greek, aged 24, was admitted to the Lakeside Hospital on Feb. 22, 1925, complaining of abdominal pain. His family history was good. He had never had any respiratory symptoms or diseases.

The present illness started ten years before, when the patient began to have recurring attacks of abdominal pain, which extended to either or both lumbar regions and to the back. The pain was severe and colicky, and would usually last for several hours. In addition to the pain, the patient also had frequency of micturition and nocturia. Hematuria did not appear until about six years after the onset of the attacks of pain, but it had recurred frequently since then. At

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3. Bradford, J. R.: Massive Collapse of the Lung as a Result of Gunshot Wounds, with Especial Reference to Wounds of the Chest, Quart. J. Med. **12**:127 (Oct.) 1918, (Jan.) 1919.

4. Hirschboeck, F. J.: Postoperative Massive Collapse of the Lungs, Am. J. M. Sc. **164**:268 (Aug.) 1922.

5. Eades, M. F.: Postoperative Massive Atelectasis: Report of Cases, Boston M. & S. J. **195**:258 (Aug. 5) 1926.

6. Tidy, H. L.: Acute Lobar Collapse of the Lung, Lancet **1**:1245, 1914.

7. Webb, G. B.; Forster, A. M., and Gilbert, G. B.: Postural Rest for Pulmonary Tuberculosis, J. A. M. A. **76**:846 (March 26) 1921.

the onset of the present illness, the attacks came on about once every three months, but they became steadily more severe and more frequent.

Physical Examination.—The patient was small but fairly well developed. The heart and lungs were normal. The results of the remainder of the physical examination were negative, except for slight tenderness in the left lumbar region.

Laboratory Observations.—The urine was cloudy and acid; its specific gravity was 1.015; the tests for albumin and for sugar were negative, and the microscopic examination showed numerous pus cells. The phenolsulphonphthalein test showed that 55 per cent of the dye was excreted in two hours and ten minutes. The blood urea was 25 mg. per hundred cubic centimeters. The blood Wassermann reaction was negative.

Roentgenograms of the urinary tract showed shadows which were suggestive of renal calculi in the region of each kidney. On the right side, there was a single large shadow; on the left side, both a large and a small shadow were present.

Cystoscopic examinations were made without general anesthesia. A moderate degree of cystitis was present. The urine from both kidneys showed numerous pus cells, and *Bacillus coli* was cultured from each specimen. One cubic centimeter of phenolsuphonphthalein was given intravenously. The dye appeared from the right kidney in four minutes and from the left in five minutes. The right kidney excreted 25 per cent of the dye in fifteen minutes, while the left excreted only 10 per cent in the same length of time. Pyelograms showed a large calculus in the pelvis of each kidney and also a small calculus in a lower calyx of the left kidney. The pelves were of normal size and shape.

Operation and Course.—On February 28, a left pyelotomy was done under nitrousoxide-oxygen and ether anesthesia. The patient was placed on his right side, and the usual position for an operation on the kidney was obtained by means of a "kidney elevator." An oblique lumbar incision was made, the kidney was freed and delivered, the posterior wall of the pelvis was opened and the stone was extracted. The time of the procedure was somewhat lengthened, because it was necessary to take roentgenograms of the delivered kidney to localize the smaller stone which was in one of the minor calyces. A small incision was made through the renal parenchyma in the attempt to locate this stone. The pelvic incision was approximated with interrupted sutures of fine catgut, and the wound was closed in the usual way with drainage of the renal fossa. The duration of the anesthesia was two hours, of which the actual operation consumed one hour and twenty minutes. There was nothing unusual about the induction of anesthesia, its subsequent course or the period of recovery. The patient's condition and color remained good throughout the entire procedure.

The patient made a good immediate recovery from the operation. Toward evening, however, his temperature began to rise, and by midnight it had reached 39.8 C. The pulse rate was 112, but the respirations remained about 22 per minute.

The next morning (March 1) the patient presented the classic picture of postoperative massive atelectasis of the right lung. The temperature was 39.4 C.; the pulse rate, 140, and respirations, 40. There was no cough, thoracic pain or sputum. The acessory muscles of respiration were being used, and the respirations were frequent and shallow. On inspection of the chest, a striking asymmetry was evident. The anterior surface of the right side of the chest from the clavicle down to the fourth rib was flattened and moved only slightly with respiration, while the same region of the left side of the chest showed a wide

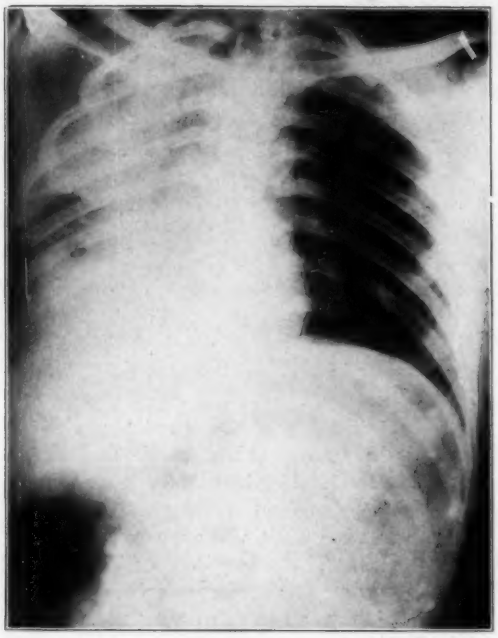

Fig. 1 (case 1).—Roentgenogram made on March 2, 1925, forty-eight hours after the first operation, a left pyelotomy. It shows a shadow of increased density in the right upper pulmonary field which has a concave lower margin and in which the pulmonary markings cannot be recognized. Below this the illumination is less impaired. The trachea and heart are displaced markedly to the right, and the right side of the diaphragm is unduly high. The left pulmonary field is translucent. The appearance is that of a postoperative massive atelectasis, largely, if not entirely, confined to the right upper lobe.

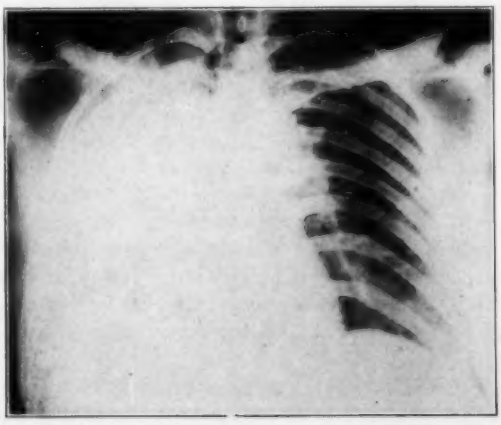

Fig. 2 (case 1).—Roentgenogram made on March 4, 1925, two days after (figure 1) showing the right upper pulmonary field a little less dense and the right lower pulmonary field much more dense than on the previous examination. The heart and trachea are still displaced to the right. The outline of the right margin of the heart and the right portion of the diaphragm cannot be identified. The left pulmonary field is normal. The appearance suggests that the lower portion of the lung is now more involved than it was, whereas the upper portion is less involved.

respiratory excursion. The vigor of movement was strikingly different on the two sides, that of the right second, third and fourth ribs being much diminished. The right costal margin moved through a greater lateral excursion than the left. The cardiac pulsation was visible 3 cm. to the right of the sternum in the second and third intercostal spaces. The upper border of hepatic flatness was at the fourth rib in the midclavicular line, and none was present in the epigastrium. The right apex was retracted, and there was dulness of the entire right lung anteriorly, most marked over the right upper lobe. In the right lower mid-axillary region, moderate tympany was present. Bronchial breathing was heard over the right apex posteriorly down to the level of the angle of the scapula, but râles were not noted. The left lung was hyper-resonant, and the breath sounds were of normal quality, but exaggerated. The left border of the heart was percussed in the fifth intercostal space 5 cm. to the left of the midline. When the patient was tested with 0.5 cc. of epinephrine hydrochloride, he was found

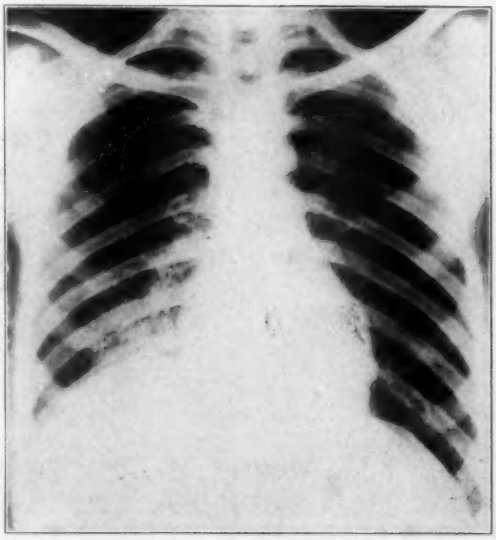

Fig. 3 (case 1).—Roentgenogram made on March 24, 1925, showing the chest normal except in the right lower pulmonary field where some increase in density and heavy pulmonary markings still persist.

to have a definite hypersensitivity. The epinephrine hydrochloride did not produce any change in his pulmonary condition.

On March 2 (second day after operation), the temperature was still elevated between 38.2 C. (100.8 F.) and 39.8 C. (103.6 F.), and the respirations were still rapid, but less than on the previous day. The heart and mediastinum were markedly displaced to the right (figs. 1 and 2). Dulness was present over the entire right lung, but râles were not heard.

On March 3 (third day after operation), the patient's condition was about the same, but, in addition, he began to cough and to expectorate a small amount of yellow, tenacious sputum.

This condition continued for one week; then the temperature came down to 38 C. (100.4 F.), and the cardiac dulness began to approach the midline. The cough and expectoration remained slight. The improvement continued, and within three weeks after the operation, the condition of the chest had returned to practically normal (fig. 3).

The patient was discharged from the hospital twenty-five days after the operation, and was told to return in about two months for removal of the calculus in the right kidney.

Second Operation.—On May 14, the patient was readmitted to the hospital for pyelotomy on the right side. He had been well, except for one attack of renal colic on the right side. He had not had any respiratory symptoms, and physical examination of the chest did not disclose any abnormalities of the heart or lungs.

Roentgenograms of the kidneys showed the calculus in the right one to be the same as on previous examinations.

A right pyelotomy was done on May 16, under nitrous oxide-oxygen and ether anesthesia. The patient was placed on his left side, and the usual position for an operation on the kidney was obtained by means of a "kidney elevator." An oblique lumbar incision was made; the posterior renal surface was freed, and the pelvis was exposed without delivering the kidney. A small longitudinal incision was made through the posterior wall of the pelvis, through which the stone was

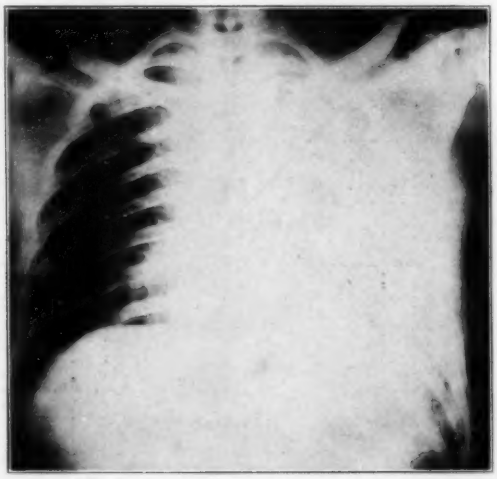

Fig. 4 (case 1).—Roentgenogram made on May 18, 1925, forty-eight hours after the second operation, a right pyelotomy. It shows a shadow of increased density occupying the entire left pulmonary field. The heart and trachea are displaced to the left. The outlines of the left margin of the heart and the left portion of the diaphragm are obliterated, but from the position of intestinal gas shadows it is evident that this side of the diaphragm is at least as high as the right. The right pulmonary field is translucent. The appearance is that of an extensive postoperative atelectasis of the left lung.

easily removed. The wound was closed in the usual way, with drainage. The total duration of the anesthesia was one hour and twenty-five minutes, whereas the operation itself lasted one hour. The anesthesia was taken well, and the patient's color and condition remained good throughout the entire procedure.

On May 17 (first day after operation), the patient's temperature rose to 39.6 C. (103.3 F.), the pulse rate was 120, the respirations were 40 and a slight cough was present. The precordial activity was marked to the left of the sternum, and the apex beat was located 1 cm. to the left of the left nipple line. The respiratory movements of the upper part of the left side of the chest were

decreased. Dulness was present over the base of the left lung posteriorly, and the breath sounds were absent. Some scattered sibilant râles were heard over the remainder of the left lung.

On the next day (May 18), the patient showed definite evidence of a post-operative massive atelectasis of the left lung. The temperature was 40 C. (104 F.), the pulse rate, 120, and the respirations, 40. Slight cyanosis was present. The cardiac activity was marked to the left of the sternum, and the apex beat was 3 cm. outside the left nipple line in the fourth intercostal space. The respiratory movements of the left side of the chest were more diminished, and the dulness at the base of the left lung was more marked. The breath sounds were absent over the left base and distant over the remainder of the left side of the chest (fig. 4).

These symptoms and signs gradually disappeared, and nineteen days after the operation the patient's temperature, pulse rate and respirations were normal, and the examination of the chest did not reveal any abnormalities. The patient was

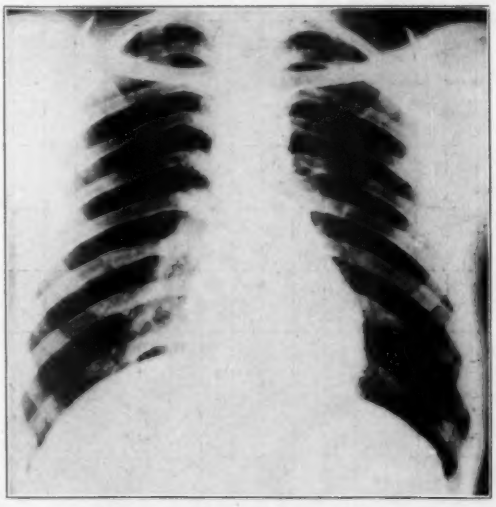

Fig. 5 (case 1).—Roentgenogram made on Oct. 8, 1925, showing essentially normal pulmonary fields except for a slight increase in density of the right base and unduly heavy pulmonary markings along the right border of the heart.

discharged on June 10 (twenty-five days after operation) feeling well and in good condition. He has been seen regularly in the follow-up clinic since then. He has not had any respiratory symptoms, and repeated examinations of the chest have not revealed any abnormalities of the heart or lungs (fig. 5).

Although we had found that the patient showed a positive reaction to the hypersensitivity test with epinephrine hydrochloride at the time of his first massive atelectasis, we wanted to discover whether he would show the same reaction when his condition was uncomplicated. Therefore, on June 28, 1927, the hypersensitivity test with epinephrine hydrochloride was repeated, and the reaction was again definitely positive (fig. 6).

In this case there are several points of interest that will be discussed later. The most obvious fact is that following a separate operation on each kidney, the patient developed massive atelectasis of the opposite

lung. Not only during the operation on the kidney was the position of the patient such that the contralateral lung was dependent, but the lumbar wound resulted in his remaining at least partially turned on the opposite side during the immediate postoperative interval in which the massive atelectasis developed. This raised the question whether there might be a correlation between the posture of the patient and the side on which localization of the massive atelectasis occurred.

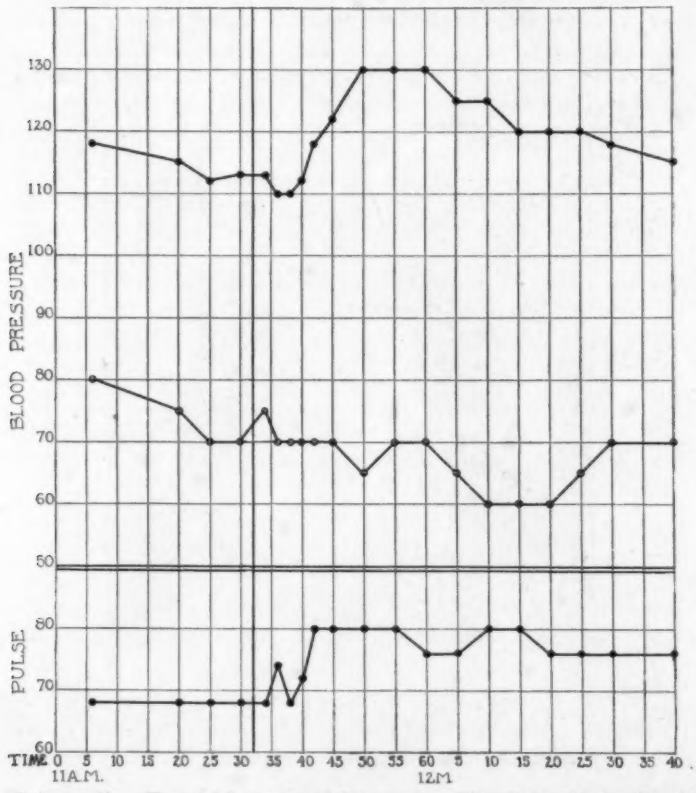

Fig. 6 (case 1).—Test of hypersensitiveness to epinephrine hydrochloride made on June 28, 1927. After control readings of the pulse rate and blood pressure were obtained (with the patient recumbent and quiet), 0.5 cc. of a 1:1,000 solution of epinephrine hydrochloride was injected subcutaneously at 11:32 a. m. There was a sustained increase in both pulse rate and blood pressure but no nervous manifestations. The patient was quiet throughout the procedure, and dozed off to sleep at 12:50 p. m. Interpretation: Definitely positive, though not extreme, hypersensitivity to epinephrine hydrochloride.

In order to determine this point, our series of twenty-two cases of postoperative massive atelectasis, studied by one or both of us in the last four years, was analyzed for the factor of posture. In most cases, the character of the operation did not necessitate lying on one side.

In two instances, however, this condition was fulfilled. Summaries of these two cases are as follows:

CASE 2.—P. J. S., an American, aged 28, was admitted to the Peter Bent Brigham Hospital, Boston, April 16, 1923, on account of dysuria of five years' duration, which was associated with hematuria and frequency of micturition. Two years after the onset of these symptoms, a typical attack of renal colic occurred on the left side and lasted several days.

The patient said that he had not had any symptoms of respiratory or cardiac disease. Physical examination gave negative results, and the chest was normal.

Cystoscopic and roentgenologic examinations revealed a moderate sized vesical calculus and a smaller calculus in the pelvis of the left kidney.

On April 18, a pyelotomy on the left side and a suprapubic cystotomy were done by Dr. Quinby under nitrous oxide-oxygen anesthesia. The patient was first placed on his right side in the usual position for an operation on the left

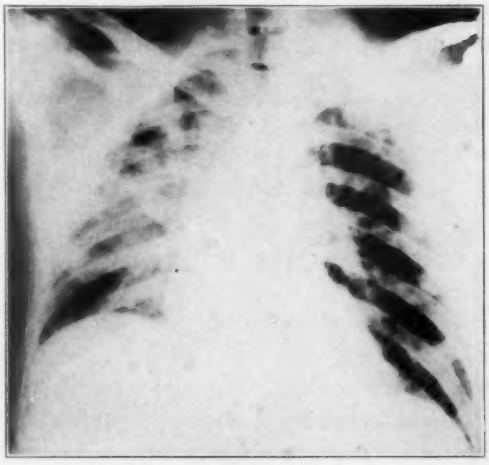

Fig. 7 (case 2).—Roentgenogram of chest made one week after a left pyelotomy, showing a diffuse mottling of the entire right lung with decreased aeration, flattening of the right side of the thorax, a high position of the diaphragm on the right side and displacement of the heart and trachea toward the right side.

kidney. After the kidney was freed and delivered, the stone was removed through an incision in the posterior wall of the renal pelvis. The wound was closed in the usual manner, with drainage. The patient was then returned to a dorsal recumbent position. Cystotomy and removal of a vesical calculus were performed, and the wound was closed in layers, the bladder being drained by an inlying catheter in the urethra. The operation and anesthesia were uncomplicated. The following day the patient's temperature, pulse rate and respiratory rate mounted, and the second day after the operation definite signs of a postoperative pulmonary complication were noted, with marked dulness and bronchial breathing over the right middle and lower lobes, but no râles. The displacement of the heart to the right was not found by physical examination but was demonstrated by the roentgenogram (fig. 7).

The patient made a good recovery from the postoperative massive atelectasis. Within eleven days after operation the temperature, pulse rate and respirations were normal, and five days later, the pulmonary signs had disappeared; a roentgenogram of the chest at this time was normal except for an accentuation in the pulmonary markings of the right lower lobe.

The patient was discharged from the hospital nineteen days after the operation, feeling well. A follow-up letter from the patient four years after his operation stated that he had not had any respiratory symptoms or diseases or urinary symptoms.

CASE 3.—E. B., a man, aged 26, was admitted to the Rochester General Hospital, Sept. 10, 1926, complaining of pain in the right sacro-iliac joint.

The results of physical examination were negative, except for tenderness over the right sacro-iliac joint. The chest was normal.

Fusion of the right sacro-iliac joint was performed by Dr. E. W. Phillips on September 11. Nothing unusual was noted in the postoperative convalescence until September 18, one week after operation, when the patient complained of cough and pain on the left side of the chest. Examination showed flattening and restricted motion in this part of the chest, flatness and diminished breath sounds at the base and a friction rub in the left axilla. Roentgen-ray examination proved the condition to be a massive collapse of the left lung. The complication did not influence the patient's convalescence from the operation.

COMMENT

These were the only cases observed by us in which massive atelectasis developed after an operation that required the patient to lie on one side. It can be seen that such conditions occur only with a limited number of operations, chiefly those on the kidney and on the sacro-iliac joint.

A search of the literature has added five more instances. Lilienthal [8] refers to a case reported by Hahn [9] in which a typical massive atelectasis developed on the left side two days after a nephrectomy on the right side for hypernephroma. The second case reported by Jackson and Lee [10] was that of a boy, aged 12, who was kept lying on his right side after laparotomy for an appendical abscess. On the third day after operation, he developed massive atelectasis of the right lung. Hunt [11] reports the case of a patient with a ruptured duodenal ulcer who was kept turned on the right side after operation in order to facilitate drainage. He developed a massive atelectasis on the

8. Lilienthal, H.: Thoracic Surgery, Philadelphia and London, W. B. Saunders Company, 1926, vol. 2, p. 86.

9. Hahn, L. J.: Massive Collapse of the Lung Following Nephrectomy, Internat. J. Med. & Surg. **37**:232, 1924.

10. Jackson, C. and Lee, W. E.: Acute Massive Collapse of the Lungs; Discussion of its Mechanism and of Its Relation to Foreign Bodies in Bronchi and Postoperative Complications, Ann. Surg. **82**:364 (Sept.) 1925.

11. Hunt, E. L.: Massive Atelectasis of Lung as Surgical Complication (case 1); Boston M. & S. J. **194**:58 (Jan. 14) 1926.

dependent side, viz., the right. Harrington [1] recorded a case of massive atelectasis on the left side which occurred the day after a nephrectomy was performed on the right side. Finally, Sante's [12] second patient presented a total massive atelectasis of the left side, which was diagnosed seven days after a nephropexy was done on the right side.

If our own cases are added to those in the literature, massive atelectasis has been seen nine times following operations that necessitate the patient's lying on his side, as shown in the table. In each instance the collapse occurred in the dependent lung. The evidence that this is not merely a coincidence is stronger for two facts: (1) in seven of the nine cases, the atelectasis occurred on the side contralateral to operation, whereas the homolateral lung is ordinarily the one involved; (2) in the majority, the collapse was on the left side, which

Total Cases of Massive Atelectasis Following Operations Which Necessitated the Patient's Lying on One Side, Including the Author's Cases and Those Reported in the Literature

Case	Operation	Dependent Lung	Side of Atelectasis
Case 1, first operation	Left pyelotomy	Right	Right
Case 1, second operation	Right pyelotomy	Left	Left
Case 2	Left pyelotomy and cystotomy	Right	Right
Case 3	Right sacro-iliac fusion	Left	Left
Hahn's case	Right nephrectomy	Left	Left
Jackson's and Lee's case 2	Laparotomy with drainage for appendical abscess	Right	Right
Hunt's case 1	Laparotomy with drainage for ruptured duodenal ulcer	Right	Right
Harrington's case	Right nephrectomy	Left	Left
Sante's case 2	Right nephrectomy	Left	Left

is the side much less commonly involved in postoperative cases. We, therefore, feel justified in concluding that when the patient has been consistently lying on one side, if unilateral massive atelectasis develops, it will occur in the dependent lung.

In most instances the patient was turned on one side both during the operation and in the postoperative period while the complication was developing. Consequently, these data do not present definite proof as to whether the effective time interval of such a postural influence is during or after the operation, or at both times.

ETIOLOGIC CONSIDERATIONS

The posture of the patient under such circumstances appears to determine the localization of the complication. It is, however, certainly not the primary cause of massive atelectasis. The simple fact that atelectasis follows only a small minority of the operations on the kidney

12. Sante, L. R.: Massive (Atelectatic) Collapse of the Lung, with Especial Reference to Treatment, J. A. M. A. **88**:1539 (May 14) 1927.

is ample evidence that there is a more fundamental factor than the position of the patient alone. From a study of the physical aspects of the condition, it is evident that there must be an obstruction at some point in the respiratory tract. The displacement of the mediastinum demonstrates an initial difference in the pressures on the two sides of this structure as conclusively as a tambour in the laboratory would show it. Certainly, this pressure would be equalized by the movement of air rather than by the great displacement of the mediastinum, if the air passage were freely open. Theoretically, this displacement of the mediastinum could be caused by an obstruction in the distended lung with an acute emphysema. The free movement, in fact the exaggerated respiratory excursion of the opposite lung, and the diminished or absent excursion of the atelectatic lung are sufficient proof that the obstruction of the air passages is on the side toward which the mediastinum is displaced. Up to this point, the evidence appears conclusive. The mechanism of unilateral postoperative massive atelectasis must include obstruction to the free exchange of air in the involved lung. Final proof of the cause and the location of this obstruction is lacking.

It is our belief that the fundamental condition which initiates massive atelectasis is a nervous reflex which affects both lungs and probably occurs frequently in a minor degree. This is suggested by many facts. In the first place, the occurrence of massive atelectasis following operations under local anesthesia and its association with trauma or spontaneous painful disease, even when the lesion is at a distance from the lung (Sante, case 1), bespeak its initiation through either the nervous or the vascular system. In the second place, as Scrimger [13] and Scott [14] have previously suggested, the number of persons with neurogenic stigmas in the group who develop postoperative massive atelectasis is apparently disproportionate. The hypersensitiveness to epinephrine hydrochloride shown by the few patients tested falls in line also with an autonomic imbalance in these persons. In the third place, our case 1 is the second one recorded in which massive atelectasis has occurred in the same patient, after successive operations. Farris [15] reported the first instance of such a case. The latter patient developed massive atelectasis on the right side after an operation for omental adhesions. A second laparotomy was necessary two months later, and again the operation was followed by massive atelectasis of the

13. Scrimger, F. A. C.: Postoperative Massive Collapse of Lung, Surg. Gynec. Obst. **32**:486 (June) 1921.

14. Scott, W. J. M.: Postoperative Massive Collapse of the Lung, Arch. Surg. **10**:73 (Jan.) 1925.

15. Farris, H. A.: Atelectasis of Lung (case 7), Canad. M. A. J. **15**:808 (Aug.) 1925.

right lung. Such cases illustrate the susceptibility of certain persons to postoperative massive atelectasis.

Perhaps the most important factor in guiding our opinion toward the reflex nature of the underlying etiologic agent was the reaction of the lung to operation, as manifested by auscultation. Our attention was first called to the rapid variation in sibilant and sonorous râles which may be heard in cases of massive atelectasis. This was described in a previous paper [14] (cases 38 and 39). Since then we have noticed it in several other instances. At some time, more commonly during the developmental period of the condition, whistling râles and squeaks much like those in an asthmatic attack were heard. These were often scattered through both sides of the chest, although they were usually more prominent in the affected side. In some instances, within half an hour or even during the same examination these sibilant râles almost entirely disappeared, but during a later examination they were again loud throughout the chest. The changes were not associated with any expectoration or moist râles during this period. Our interpretation of the rapid appearance and disappearance of sibilant râles was that in both lungs the lumina of the finer air passages were undergoing variations in size, resulting from alterations in bronchomotor or vasomotor tone. After observing this phenomenon in definite cases of massive atelectasis, we desired to determine whether evidence of such a reflex could be obtained in uncomplicated postoperative cases. Three patients with inguinal hernia, operated on under local anesthesia, were carefully examined before and after operation. In two of the three, sibilant râles developed at times and were heard over both lungs posteriorly. These râles also appeared and disappeared. They were much less pronounced than those in cases of atelectasis, but they were of a similar character and did not resemble the crepitant râles heard over the edge of the lung when it expands on the deepening of respiration. The râles were heard best from twenty-four to thirty-six hours after operation. Similar râles were not caused merely by recumbency without operation. It was our impression, then, that a simple operation under local anesthesia (at least in some cases) had caused a bilateral reflex narrowing of the smaller air passages. It is extremely difficult to get absolute proof of this action, but such an hypothesis seems to offer the best explanation of the clinical observations.

If the primary causative agency in the production of massive atelectasis is a bilateral reflex, how is the usual striking unilateral form of the condition produced? The answer to this question is twofold. First, perhaps the more common form of this condition is not the massive unilateral atelectasis, but the less extensive bilateral condition. Evidence that the latter is an important and serious postoperative pulmonary complication is gradually accumulating, although it is much

more difficult to diagnose clinically than the unilateral type (Bergamini and Shepard [16] and Hirschboeck [4]). It may be that most of the conditions now diagnosed as postoperative bronchopneumonia will be found to arise as bilateral lobular atelectatic areas, just as unilateral massive atelectasis was not until recently differentiated from postoperative pneumonia. In the second place, while the initiating reflex condition is bilateral, unless the obstruction of the air passages in a part of the lung becomes complete or acts as a reverse check valve (thus, allowing air to pass out of, but not into, the lung), massive atelectasis in its recognized unilateral clinical form will not occur. Undoubtedly, there are secondary factors which influence the completeness of the obstruction. One of these, we believe that we have demonstrated to be a continued unilateral posture of the patient. If massive atelectasis occurs, the dependency of one lung for some reason causes the localization of the process in this side. The mechanism that causes this localization has not been demonstrated. The initial reflex is probably vasodilative in character. The most striking histologic feature found post mortem in massive atelectasis is an extreme pulmonary congestion, almost an angiomatous condition (Bradford,[3] Santee,[17] and Bergamimi and Shepard [16]). This is probably the one outstanding difference in the lung between postoperative massive atelectasis and pulmonary collapse caused by the pressure of a hydrothorax or pneumothorax. Quite possibly, obstruction becomes complete on the dependent side in massive atelectasis because of greater congestion in the dilated pulmonary capillaries. By whatever method posture induces localization of the atelectasis, however, it may play a rôle even in patients who are placed on their backs. It is much easier for most patients to roll on their right side after laparotomy, especially after the more common incisions on the right side of the abdomen. In a former paper [14] (figs. 5 and 6, 1925), the position that these patients with massive atelectasis assume for comfort was illustrated. It was presented to show why the asymmetry of the chest and of the respiratory excursion was not at once obvious. It is possible, however, that this position, which may mask detection of the condition and which is assumed for comfort, may also be responsible for the localization of the pulmonary lesion. The cases of contralateral collapse which were extremely common following wounds of the chest (Crymble [18]) may well be examples of this suggestion that a

16. Bergamini, H., and Shepard, L. A.: Bilateral Atelectasis (Massive Collapse) of Lung, Ann. Surg. **86**:35 (July) 1927.

17. Santee, H. E.: Bilateral Massive Collapse of Lung, Ann. Surg. **85**:608 (April) 1927.

18. Crymble, P. T.: Gunshot Wounds of the Chest. Brit. J. Surg. **5**:363 (Jan.) 1918.

unilateral posture determines the localization of atelectasis in the dependent lung.

An obvious corollary to this idea of the influence of posture is that after operation the patient should not be allowed to remain constantly in one position. He should be turned from side to side so that the dependency of one lung does not occur, particularly during the immediate postoperative period.

Undoubtedly, other secondary factors besides posture greatly hasten the completion of the obstruction of the smaller air passages. Jackson and Lee have particularly stressed the secretion of a thick tenacious mucus. This is probably one of the most important elements in the completion of the obstruction, although we feel that the obstruction is in the small peripheral air passages rather than in the main bronchi. A diminution in the respiratory force may be another important factor.

When, by these processes, a major portion of one lung is shut off from respiratory exchange, it soon becomes atelectatic, and a compensatory factor affects the process in the remaining lung. It is a common observation that as the respiratory excursion of the atelectatic lung diminishes, that of the other lung increases. In our opinion, this is due to a compensatory hyperventilation of this lung which, in spite of the initial bilateral pulmonary reflex, prevents the development of any serious obstruction in the small respiratory passages of the second side.

Our conception of the development of unilateral massive atelectasis is, then, as follows: 1. Initial pulmonary reflex, (probably vasomotor) causes bilateral partial obstruction in the peripheral respiratory passages. 2. Secondary factors, such as position and tenacious secretion, make this obstruction complete on one side in advance of the other. 3. When this occurs on one side compensatory hyperventilation of the other side keeps these latter respiratory passages open (should this not occur, bilateral atelectasis is produced). 4. The air on the side of the bronchiolar occlusion is absorbed within a few hours (or more rarely may possibly be exhausted by a reverse check-valve obstruction (Jackson and Lee [19]), and the complete picture of a unilateral massive atelectasis develops.

SUMMARY

1. A case is reported in which contralateral postoperative pulmonary massive atelectasis developed after separate successive operations on each kidney.

2. Nine instances of unilateral massive atelectasis have been assembled in which the patient had been lying consistently on one side. The posture of the patient seemed to determine the localization of the condition which was uniformly in the dependent lung.

19. Jackson and Lee (footnote 10, p. 386).

3. Observations are presented favoring the view that the initial etiologic factor in massive atelectasis is a nervous reflex affecting both lungs. Secondary factors then determine the unilateral localization.

NOTE.—Since writing this article we have learned of direct measurements of the intrapleural pressure in massive atelectasis by Elkin.[20] These express numerically the greater negative intrathoracic pressure on the atelectatic side which is shown qualitatively by the displacement of the mediastinum.

20. Elkin, Dan C.: Ann. Surg., in press.

DISTRIBUTION OF THE SYMPATHETIC RAMI TO THE BRACHIAL PLEXUS

ITS RELATION TO SYMPATHECTOMY AFFECTING THE UPPER EXTREMITY *

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ST. LOUIS

Extirpation of the stellate ganglion or section of the gray rami which connect this ganglion with the brachial plexus has become a recognized surgical procedure, especially in diseases involving the blood vessels of the upper extremity. The aim of this procedure in diseases of the blood vessels is vasomotor denervation of the extremity. Extirpation of the stellate ganglion alone, or section of the gray rami which connect it with the brachial plexus, however, does not completely eliminate the sympathetic nerves of the upper limb in a large percentage of cases. The operation has failed to produce the desired results in certain cases, probably because of incomplete sympathetic denervation of the blood vessels which were involved.

During the progress of studies involving the gray rami associated with the brachial plexus and the distribution of sympathetic fibers in the upper extremity, my attention was called to the inconstant intrathoracic ramus that connects the first and second thoracic nerves as a possible pathway through which sympathetic fibers that leave the sympathetic trunk below the stellate ganglion might enter the first thoracic nerve and become incorporated in nerves arising from the brachial plexus. Accordingly, the present study of the lower cervical and upper thoracic portions of the sympathetic trunks and the communicating rami joining the spinal nerves which contribute to the innervation of the upper extremity was undertaken in order to obtain more exact knowledge regarding the sources of the sympathetic innervation of the upper limb and, if possible, to afford a rational basis for an operative procedure that will in all cases effectively deprive the blood vessels of this limb of their vasomotor nerves.

The chief sources of sympathetic fibers to the upper extremity are the middle cervical and stellate ganglions. These ganglions, as well as the upper thoracic sympathetic ganglions, are extremely variable. Not infrequently the middle cervical ganglion is absent; when it is present, it is generally located about the level of the body of the sixth cervical vertebra. It is usually connected through the gray rami with the fifth

* From the St. Louis University School of Medicine.

and sixth cervical nerves; in some instances, also with the fourth and seventh cervical nerves (Potts, 1925).[1] In some instances the middle cervical ganglion lies close to the stellate ganglion. In such cases, the communicating rami arising from the cervical sympathetic trunk may join the fifth and sixth and possibly the fourth and seventh cervical nerves.

A discrete, inferior, cervical sympathetic ganglion occurs but rarely, if at all, in man. This ganglion commonly fuses with the first thoracic sympathetic ganglion to form a stellate ganglion. In some instances the second thoracic sympathetic ganglion is also incorporated in the stellate ganglion. This ganglion varies greatly in size and form. It commonly lies about the level of the neck of the first rib, but it may occupy a somewhat lower position. Gray rami arising from the stellate ganglion join the seventh and eighth cervical and the first thoracic nerves. Not infrequently, especially if the middle cervical ganglion is absent, a gray ramus from the stellate ganglion joins the sixth cervical nerve. At times the stellate ganglion sends a gray ramus to the second thoracic nerve. The first thoracic nerve also sends a white ramus into the stellate ganglion.

Although an intrathoracic ramus of the second thoracic nerve joins the first thoracic nerve in a large percentage of cases, the second thoracic nerve is not commonly regarded as contributory to the brachial plexus. In forty-eight cadavers examined during the present study, an intrathoracic ramus connecting the first and second thoracic nerves was present bilaterally in twenty-one and unilaterally in nine. In the twenty-one cadavers in which it was present bilaterally, this ramus was described as large in ten, of medium size in seven and as small in four. In the nine cadavers in which it was present on only one side, it was described as of medium size in five and as small in four.

According to statements in the textbooks regarding this inconstant ramus of the second thoracic nerve, it may join only the intercostal ramus of the first thoracic nerve or only the brachial plexus, or it may contribute fibers to both the first intercostal nerve and the brachial plexus. In the cadavers examined in the present study, this ramus joined the first intercostal nerve distal to its origin from the first thoracic nerve in only six cases, in all of which it was described as medium or small. In all the other cases it joined the first thoracic nerve proximal to the origin of the first intercostal nerve. If the ramus in question is small, all of its fibers may still be incorporated in the first intercostal nerve, although a contribution of fibers from the second thoracic nerve to the brachial plexus is not precluded. Not infrequently

1. Potts, T. K.: The Main Peripheral Connections of the Human Sympathetic Nervous System, J. Anat. **59**:129, 1925.

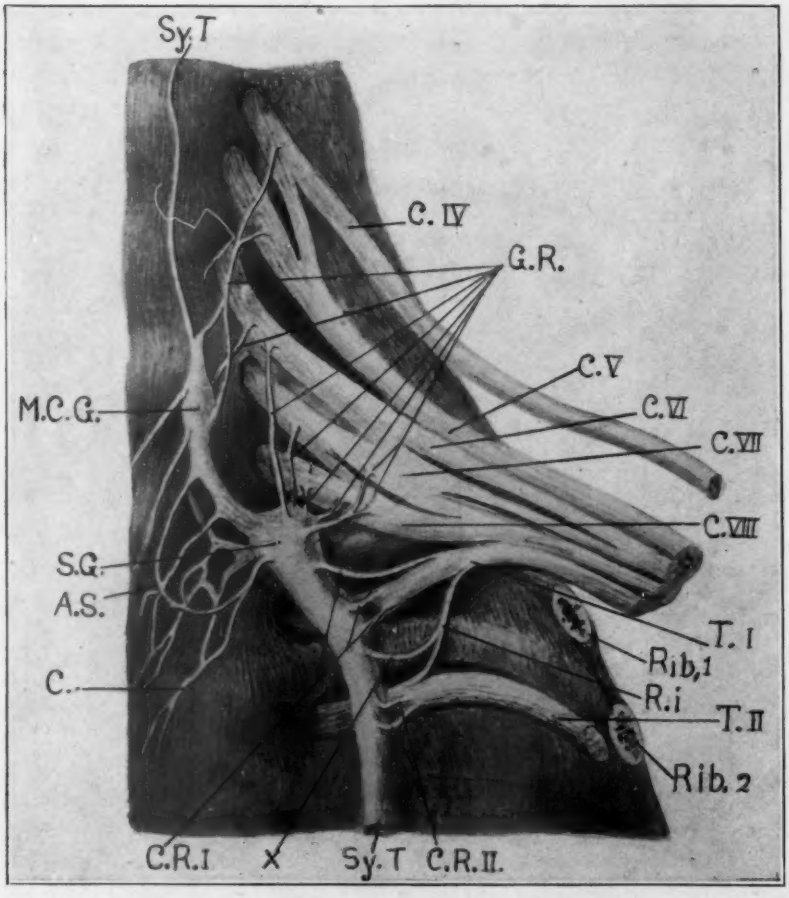

Fig. 1.—Drawing from the cadaver to illustrate the inconstant intrathoracic ramus from the second to the first thoracic nerve and the communicating rami joining the brachial plexus. In the illustrations, *A. S.* indicates the ansa subclavia; *C.*, the cardiac nerves; *C. IV* to *C. VIII*, cervical nerves; *C. R. I*, communicating rami to first thoracic nerve; *C. R. II*, communicating rami to second thoracic nerve; *G. R.*, gray communicating rami to cervical nerves; *M. C. G.*, middle cervical ganglion; *R. i*, inconstant intrathoracic ramus from second to first thoracic nerve; *S. G.*, stellate ganglion; *Sy. T.*, sympathetic trunk; *X*, sympathetic ramus joining the ramus from the second to the first thoracic nerve; *T. I*, first thoracic nerve; *T. II*, second thoracic nerve.

this ramus is actually larger than the first intercostal nerve. In such instances, the second thoracic nerve clearly contributes fibers to the brachial plexus.

The second thoracic nerve is commonly connected with the second thoracic sympathetic ganglion or the sympathetic trunk by a white and a gray ramus. In some of the cases in the present study, a gray ramus from the second thoracic sympathetic ganglion or the sympathetic

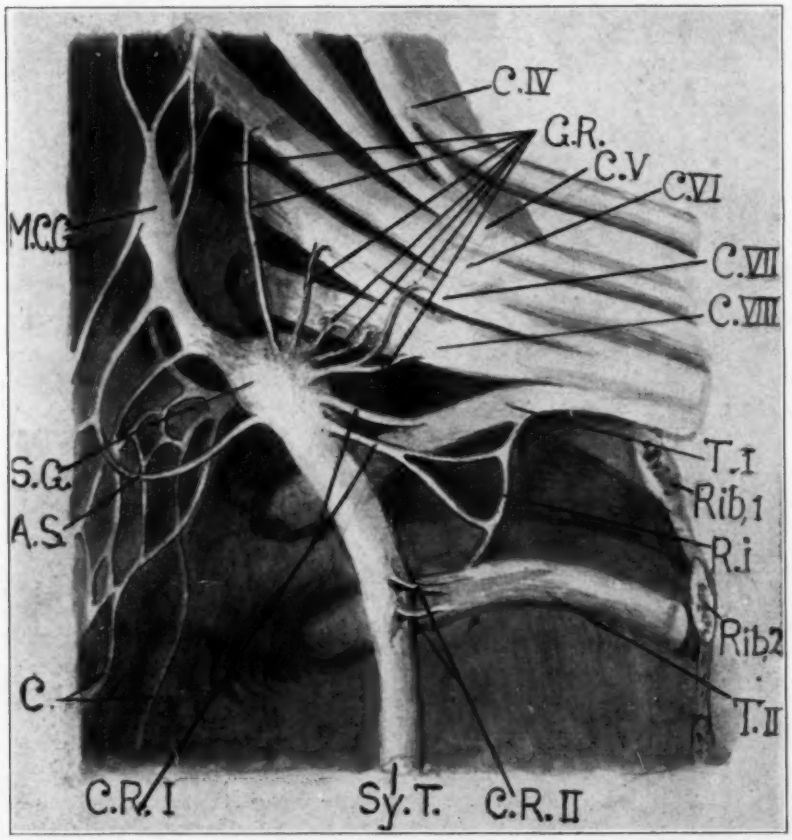

Fig. 2.—Drawing from the cadaver to illustrate variation in the inconstant intrathoracic ramus from the second to the first thoracic nerve.

trunk was traced directly into the ramus connecting the first and second thoracic nerves (fig. 1 *x*). In other cases a ramus from the stellate ganglion was also traced into this ramus. In all cases in which a gray ramus was traced from the second thoracic ganglion or the sympathetic trunk directly into the ramus joining the first thoracic nerve, one or more communicating rami also joined the second thoracic nerve. Not infrequently, a communicating ramus joined the second

thoracic nerve at or near the point of origin of the ramus that joins the first thoracic nerve. Sometimes it was apparent that some of the fibers in the communicating ramus joined the ramus leading to the first thoracic nerve. In a few instances, a small ramus was traced into the first thoracic nerve directly from the second thoracic sympathetic ganglion or the communicating ramus connecting this ganglion with the second thoracic nerve. Figure 3 illustrates a large intrathoracic ramus that arises from the second thoracic nerve farther distally than usual,

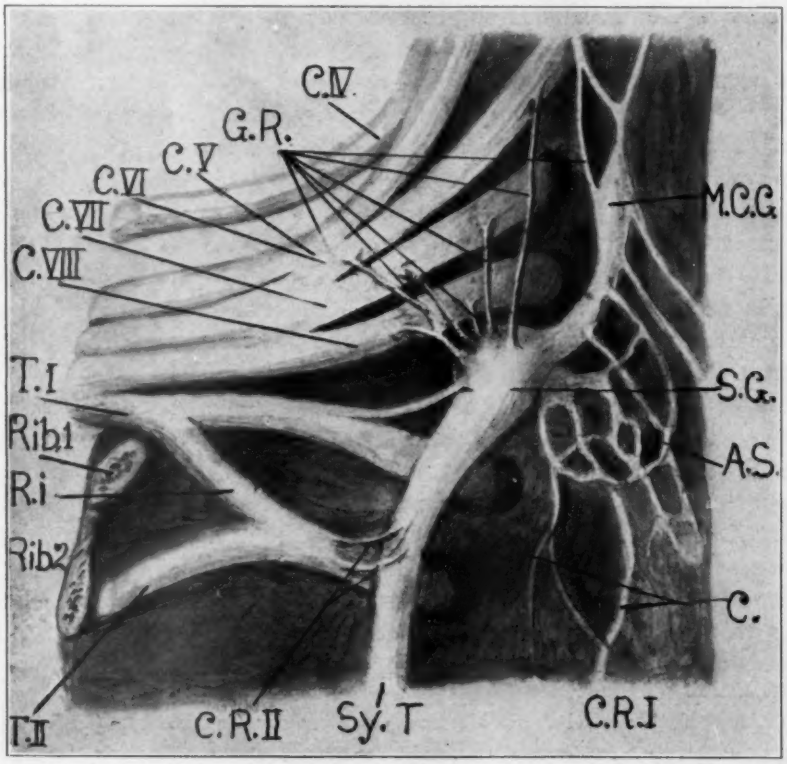

Fig. 3.—Drawing from the cadaver to illustrate a very large intrathoracic ramus from the second to the first thoracic nerve.

but joins the first thoracic nerve proximal to the origin of its intercostal ramus.

Microscopic study of sections of the intrathoracic ramus joining the first and second thoracic nerves taken at autopsy in two cases in which this ramus was well developed revealed that myelinated fibers occur there more frequently than they do in sections of spinal nerves distal to the communicating rami. Fibers of small caliber with thin myelin sheaths occur in abundance in these sections; thinly myelinated fibers

of small caliber also occur in abundance in sections of the gray rami in these cases. These observations regarding the frequency of unmyelinated fibers in the ramus joining the first and second thoracic nerves in man were corroborated in sections of this ramus taken from animals (cats and dogs). While a small caliber and a thin myelin sheath or complete absence of myelin are not absolute criteria of the sympathetic nature of nerve fibers, the majority of these fibers in the ramus doubtless are sympathetic.

The foregoing observations show clearly that the intrathoracic ramus connecting the first and second thoracic nerves, which is present in man in a large percentage of cases, contains sympathetic fibers. Whenever this ramus joins the first thoracic nerve proximal to the origin of the first intercostal nerve it constitutes a pathway through which sympathetic fibers that leave the sympathetic trunk below the stellate ganglion enter the brachial plexus.

Recent studies of the innervation of the arteries of the extremities in mammals (Hirsch, 1925;[2] Wiedopf, 1925,[3] and Kerper, 1927)[4] show clearly that sympathetic fibers which are carried peripherally in the larger nerve trunks join the arteries at intervals along their course. Sympathetic fibers reach the vessels of the extremities mainly via these nerves. Few if any sympathetic fibers extend peripherally along the walls of the vessels. The nerves that supply the voluntary muscles include not only the sympathetic fibers which, as shown by Boeke (1913, 1927)[5] and others, terminate on striated muscles, but also sympathetic fibers which supply the blood vessels in the muscle (Kuntz 1927).[6] As the first thoracic nerve contributes largely to both the median and ulnar nerves, the sympathetic fibers contained in it, including those which enter via the ramus from the second thoracic nerve whenever this ramus is present, are relatively widely distributed to blood vessels and other tissues in the upper extremity.

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2. Hirsch, L.: Ueber die Nervenversorgung der Gefässe im Hinblick auf die Probleme der periateriellen Sympathektomie, Arch. f. klin. Chir. **137**:281, 1925.

3. Wiedopf, O.: Der Verlauf der Gefässnerven in den Extremitäten und deren Wirkung bei der periarteriellen Sympathektomie, München. med. Wchnschr. **72**:413, 1925.

4. Kerper, A. H.: The Innervation of the Arteries of the Extremities, Thesis, to be published.

5. Boeke, J.: Die doppelte (motorische und sympathische) efferente Innervation der quergestreiften Muskelfasern, Anat. Anz. **44**:343, 1913. Die morphologische Grundlage der sympatischen Innervation der quergestreiften Muskelfasern, Ztschr. f. mikr-anat. Forsch. **8**:561, 1913.

6. Kuntz, A.: On the Occurrence of Sympathetic Nerve Fibers in Muscles of the Extremities Following Experimental Degeneration of the Spinal Nerves, J. Comp. Neurol., 1927, vol. 43.

In view of the foregoing anatomic data, extirpation of the stellate ganglion or section of the gray rami connecting this ganglion with the brachial plexus is inadequate to insure complete sympathetic denervation of the blood vessels of the upper extremity in cases in which the inconstant intrathoracic ramus connecting the first and second thoracic nerves is present. In such cases, complete sympathetic denervation of the upper extremity requires extirpation of the stellate ganglion and of the upper portion of the thoracic sympathetic trunk to the level below the communicating rami of the second thoracic nerve, or section of the communicating rami of the second thoracic nerve and any peripheral rami arising from the thoracic sympathetic trunk above this level, in addition to section of the gray rami connecting the stellate and middle cervical ganglions with the brachial plexus.

EXOPHTHALMIC GOITER

PATHOLOGIC CHANGE AS A RESULT OF THE ADMINISTRATION OF IODINE (LUGOL'S SOLUTION)*

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As early as 1600 B. C., the Chinese used the ash of seaweed and sponges in the treatment of goiter empirically. The use of iodine in this form continued through ancient, medieval and modern times until the introduction of the pure drug in the treatment of the thyroid gland by Coindet in 1820, which followed closely the isolation of iodine from the ash of burnt sponges and seaweed by Fyfe. Coindet reported excellent results following the administration of from five to twenty drops of the tincture daily. France used iodine extensively in the Department of the Seine about 1853. It was used in the form of a powder in the food or as an ointment, which is an interesting example of the popular use of iodine at this time. Baumann discovered that iodine was a normal constituent of the thyroid gland in 1895, and this gave a more reasonable basis for its use.

Wharton, in 1656, gave the first satisfactory description of the thyroid gland and named it. A century previously, Vesalius had described the gland, and some knowledge of the external deformity and clinical symptoms of thyroid disease was prevalent among the ancients. The Romans during the time of Caesar believed that a large neck was characteristic of the Gauls and it was recognized that slaves with bulging eyes fatigued easily. The ancients of this period, however, failed to recognize the thyroid gland as different from other glands of the neck and spoke of the enlargement as bronchocels.

Parry, in 1786, first described exophthalmic goiter; it was described by Graves in 1836 and by Basedow in 1840. This was the most important advance in clinical differentiation until the present time, and ranks with Baumann's discovery of the presence of iodine in the thyroid gland as a necessary step in the later rational use of iodine in the treatment of goiter.

The mortality rate attending thyroidectomy was at first high, but was later greatly reduced through the efforts of Theodor Kocher, C. H. Mayo, Halsted, Crile, Ochsner, H. S. Plummer and others.

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Plummer,[1] in 1913, published important data on the clinical and pathologic relationship of exophthalmic goiter. He differentiated exophthalmic goiter and hyperfunctioning adenomatous goiter, and thus established the clinical foundation for the advantageous use of iodine.

Kendall[2] isolated thyroxin as a pure chemical compound in 1914. Plummer, in 1922, introduced iodine in the form of Lugol's solution in the preoperative and postoperative treatment of patients with exophthalmic goiter, starting its use at a time when iodine for this purpose was considered inadvisable and dangerous. By differentiating adenomatous goiter with hyperthroidism and exophthalmic goiter, Plummer had made it possible to avoid the danger of indiscriminate use of iodine and its subsequent bad results in cases of adenomatous goiter. The lack of this differentiation had been a stumbling block in the progress of treatment by iodine and had been partially responsible for its unpopularity. The use of iodine in the treatment of exophthalmic goiter was the result of observations begun by Plummer in 1913. In an article published in 1925 he says, "While preparing an article for publication in Oxford Medicine, I suddenly became convinced that there are many reasons why the action of iodine might have been misinterpreted. The chief of these was the lack on the part of observers of a correlation of the fluctuating findings throughout the course of the disease on a clear-cut hypothesis of the presence of two factors whether or not the factors are two products of the thyroid gland."[3]

The theory on which Plummer first used iodine was based on the assumption of two thyroid secretions in cases of exophthalmic goiter, the first a normal secretion, the second an abnormal one, the normal secretion causing the symptoms of hyperthyroidism, the abnormal causing the characteristic toxic symptoms and the ratio between the two secretions varying at different times in the course of the disease, being influenced by the amount of iodine present, the degree of stimulation, the training and fatigue of the thyroid gland and probably unknown factors. With regard to the training of the gland, Plummer writes: "The hypothesis that periods of intensive stimulation alternating with periods of remissions, provided exacerbations and remissions happened to be favorably timed, will cause a physiologic as well as an anatomic hypertrophy of the thyroid has, like most of the hypotheses presented in

1. Plummer, H. S.: The Clinical and Pathological Relationship of Simple and Exophthalmic Goiter, Am. J. M. Sc. **146**:790-795, 1913.

2. Kendall, E. C.: The Isolation in Crystalline Form of the Compound Containing Iodin which Occurs in the Thyroid: Its Clinical Nature and Physiological Activity, Tr. A. Am. Phys. **30**:420-449, 1915.

3. Plummer, H. S.: The Function of the Thyroid Gland, Collected Papers of The Mayo Clinic and The Mayo Foundation **17**:473-499, 1925.

this paper, been daily checked against the findings of the disease in the analysis of cases under observation." [4]

Plummer writes with regard to iodine: "Many reactions that might follow the administration of iodine were considered. The complete iodinization of the thyroxin molecule in the tissues of the body seemed possible but not probable. That the iodine might lead to more complete iodinization of thyroxin in the gland or that it might block its discharge seemed more probable.....Irrespective of the degree of stimulation the thyroid will not elaborate much of the abnormal secretion if a sufficient amount of the iodine is available." [3]

The pathology of exophthalmic goiter has been well described by MacCallum,[5] Wilson,[6] Hämig [7] and others who supported the view that there are constant pathologic features and by Virchow, Kocher and others who opposed this view.

Marine's [8] work on the relationship of iodine to the prevention of hyperplastic changes in the thyroids of dogs, following resection of part of the gland and the relationship of iodine to the hyperplasia of exophthalmic goiter; that of Halsted, Victor Horsley [9] and others on the hypertrophy of the thyroid following the removal of part of the gland, with Halsted's [10] observation that if the gland of a female dog is removed before pregnancy the pups at birth will have enlarged thyroids; the work of Giordano and Caylor,[11] who in studying the thyroids removed after ligation of the superior thyroid artery found that there

4. Plummer, H. S.: Functions of the Normal and Abnormal Thyroid Gland, Oxford Medicine, New York, Oxford University Press, 1921, vol. 3, pp. 839-873.

5. MacCallum, W. G.: The Pathology of Exophthalmic Goiter, J. A. M. A. **49**:1158-1162 (Oct. 5) 1907.

6. Wilson, L. B.: The Relationship of the Clinical and Pathologic Aspects of Exophthalmic Goiter, Northwest. Med. **5**:1-5, 1913; The Pathology of the Thyroid Gland in Exophthalmic Goiter, Am. J. M. Sc. **146**:781-790, 1913; Notes on the Pathology of Simple and Exophthalmic Goiter, M. Rec. **84**:373-378, 1913; A Study of the Pathology of the Thyroids from Cases of Toxic-Non-Exophthalmic Goiter, Journal-Lancet **34**:93-97, 1914.

7. Hämig, Gottfried: Anatomische Untersuchungen über Morbus Basedowii, Arch. f. klin. Chir. **55**:1-68, 1897.

8. Marine, David: On the Occurrence and Physiological Nature of Glandular Hyperplasia of the Thyroid (Dog and Sheep) Together with Remarks on Important Clinical Human Problems, Bull. Johns Hopkins Hosp. **18**:359-364, 1907.

9. Horsley, Victor: The Pathology of the Thyroid Gland, Brown Lectures, Lancet **2**:1163-1164, 1886.

10. Halsted, W. S.: An Experimental Study of the Thyroid Gland of Dogs with Special Consideration of Hypertrophy of this Gland, Rep. Johns Hopkins Hosp. **1**:373-422, 1896.

11. Giordano, A. S., and Caylor, H. D.: Histological Study of the Effect of Ligation of the Thyroid Vessels in Exopthalmic Goiter, Surg. Gynec. Obst. **36**:75-80, 1923.

are changes at the superior pole of the gland similar to those described by Marine in the hyperplastic glands of dogs and sheep following the administration of iodine, and the excellent results obtained by Plummer [12] following the administration of iodine preoperatively to patients with exopthalmic goiter (thus lowering the surgical mortality from 3.5 to 1 per cent, and causing the almost complete cessation of preoperative ligation) led to the present study to determine whether these thyroids were showing histologic changes as a result of this treatment.

The thyroid gland which has undergone the characteristic exophthalmic changes is slightly larger, and there is an increase in the vascularity and an increase in the stroma, especially late in the sequence, as pointed out by Marine. There is an increase in the number of the cells lining the acini which varies greatly in different glands and often in the same gland, and a change in type from cuboidal to columnar in the epithelial cells lining the acini. There is an infolding which produces hillock-like elevations into the acini, or sharp projections. The colloid is less than in the normal gland and may be almost absent. In the lumen of various acini, spriglike processes, as described by MacCallum and Wilson, are found. Scattered throughout the gland are numerous lymphocytic cells which may be arranged in the form of a lymphoid nodule or be present in areas without apparent arrangement. Macroscopically the superficial blood vessels appear larger than in the normal gland. The cut surface appears "meaty" with a fine lobulation.

Previous to this study, Broders had noted a change in the thyroid glands which were brought to his laboratory for diagnosis following the administration of Lugol's solution. The frozen section showed less columnar epithelium and hyperplasia, and there was more difficulty in making a diagnosis. At this time also, clinical results pointed to a change in the gland. Plummer noted: "The disappearance of the characteristic nervous phenomena including the crisis death, cessation in the development of exophthalmos and in some cases rapid regression with a reduction of the entire physiologic status to that of hyperfunctioning adenomatous goiter, except for the anatomic findings in the thyroid, the exophthalmos and minor physical findings which remain an index of the preexisting status unless the patient is too near a moribund state before iodine is started." [3]

With the disappearance of the toxic symptoms the basal metabolic rate began to drop; this led Plummer to conclude that the abnormal product had a catalytic action. Cases, however, in which the symptoms were due apparently to an excess of thyroxin alone showed little change in the clinical picture or metabolic rate. Plummer said: "No drop of

12. Plummer, H. S., and Boothby, W. M.: The Value of Iodin in Exophthalmic Goiter, J. Iowa M. Soc. **14**:66-73, 1924.

basal metabolism is obtained in those cases with high basal metabolic rates and in which the clinical picture is entirely attributable to an excess of thyroxin in the body, however, there is some evidence that iodine temporarily to a degree checks delivery of thyroxin." [3]

This remarkable change in the patient was accompanied by a palpable change in the thyroid gland on physical examination. The change in the clinical picture, falling metabolic rate, relief of toxic symptoms, improvement in the general condition and palpable change in the gland suggested an anatomic condition less active than that before the administration of the iodine. The cases in which the basal metabolic rate did not fall, showing little change clinically, were not investigated separately. It is probable, however, judging from this study, that active hyperplasia and hypertrophy of the gland remain.

It was realized, as pointed out by Wilson,[13] that the only way in which the problem could be approached without laying oneself open to erroneous conclusions due to changes in the gland brought about by remissions; erroneous clinical diagnoses; previous iodinization in the supposedly noniodinized cases; the possibility that individual thyroids do not absorb iodine in like amounts with similar results and other unknown causes was by a comparative study of the glands in a large number of cases, in some of which iodine had been given. Hyperplastic glands were chosen in cases in which exophthalmic goiter had been diagnosed previous to operation and which were free from adenomas large enough to cause recognizable deformity macroscopically, and relatively free from small adenomas only detectable microscopically. This selection of glands reduces the percentage error from wrong diagnoses to a fraction of 1 per cent, according to Plummer.

The method followed in this series was to study the epithelium of the acini, the connective tissue, blood vessels and lymphocytic cells of the stroma and the colloid found in the acini, and to compare and contrast the results (with and without the administration of iodine). Paraffin sections of 200 thyroids were studied; 100 of the patients had received Lugol's solution and 100 had not. Only those glands which showed pathologic changes characteristic of exophthalmic goiter as mentioned were selected. The pathologic changes were graded on a basis of 1 to 4. All the thyroids were, in this manner, divided into four groups, 1, 2, 3 and 4. The grade represents a quantitative estimate of the extent of pathologic change as shown in the table. As an example, in a case in which iodine had been given colloid was graded 4, meaning that the gland belonged to the group containing the most colloid; hyperplasia was graded 1, columnar epithelium was graded 1 and the number

13. Wilson, L. B.: Personal communication to the author.

of lymphocytes was graded 1, meaning that in these three histologic details the gland belonged to the group showing the least pathologic change of all the four groups. The figures are plotted in curves to show the results graphically (figs. 1, 2 and 3).

The results of animal experimentation are discussed in the consideration of the results obtained by a study of this series of cases, but it should be held clearly in mind that the only relationship is an anatomic similarity, and the fact that in both cases iodine had been given. The fact that iodine in both cases is associated with similar anatomic changes gives a false impression of an identity of physiologic processes for which there is so far no proof. The animal experimentation has been carried out under conditions which produced iodine deficiency or glandular deficiency, while the physiology of exophthalmic goiter is much more complicated and deals with many physiologic processes, yet

Effect of Administration of Iodine on Grading of Amount of Colloid and Degree of Hypertrophy and Hyperplasia in Thyroid Glands *

	Iodine Administered			No Iodine Administered		
Grade	Colloid (Thyroid)	Hypertrophy (Thyroid)	Hyperplasia (Thyroid)	Colloid (Thyroid)	Hypertrophy (Thyroid)	Hyperplasia (Thyroid)
4	76	..	..	12	14	48
3	22	14	14	14	36	18
2	2	18	34	26	28	18
1	..	58	52	48	22	16

* Lymphocytic tissue is much the same in both groups. There is too little increase in this series to justify a statement.

unknown, as etiologic factors. Giordano's and Caylor's work on ligated thyroids is also discussed. Here again the inclusion has only an anatomic basis, except for the clinical fact that preoperative ligation is rarely necessary since the introduction of iodine.

CHANGE IN AMOUNT OF COLLOID

The most noticeable change in the thyroids after the administration of iodine is the increase in the amount of colloid. A typical thyroid in exophthalmic goiter, as has long been recognized, has little colloid. The amount of colloid may be so increased as to give a histologic picture similar to that of colloid goiter in which there are hyperplastic areas. The colloid in these thyroids also stains lighter and does not present the vacuolated appearance that is found in cases of exophthalmic goiter in which iodine has not been given (figs. 4 and 5). The cut surface of these glands is similar to colloid glands macroscopically. The follicles are filled with clear viscid colloid which makes the gland appear translucent and a lighter red.

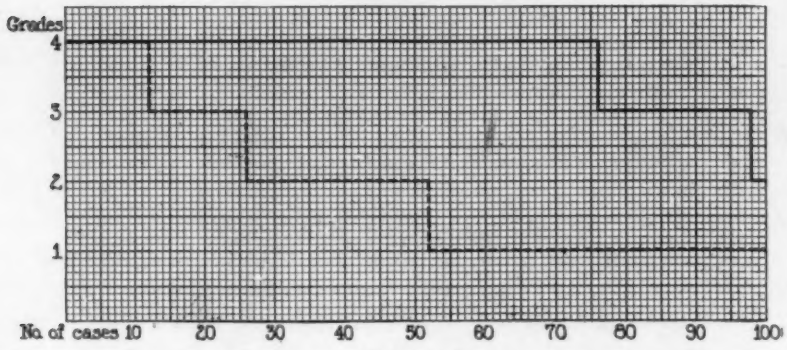

Fig. 1.—Comparative amounts of colloid in the thyroid glands in cases of exophthalmic goiter in which iodine was and was not administered; in this and the following figures the solid line represents the number of glands and grading when iodine was given, and the broken line when it was not given.

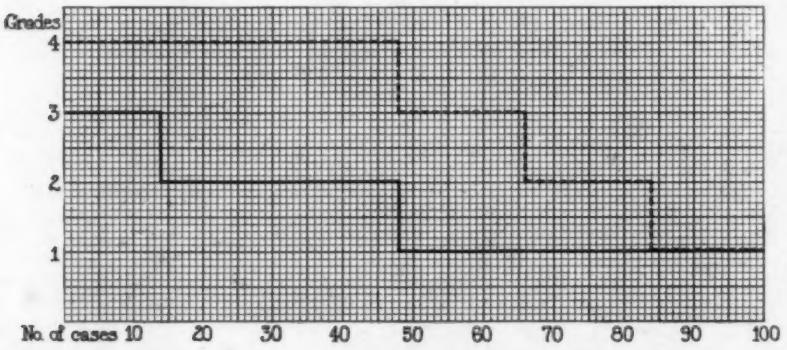

Fig. 2.—Comparative degrees of hyperplasia of the thyroid gland in cases of exophthalmic goiter in which iodine was and was not administered.

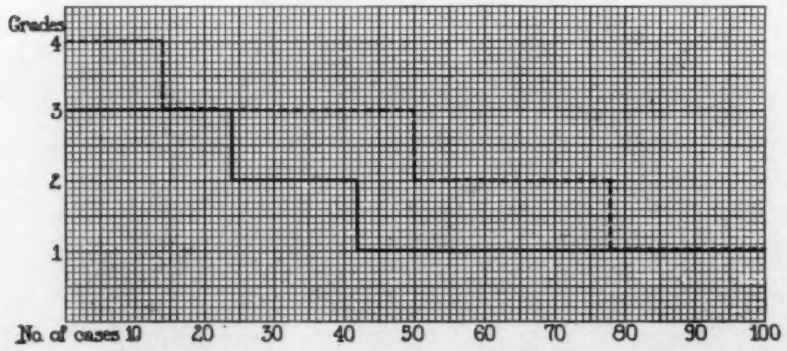

Fig. 3.—Comparison of the amount and extent of columnar epithelium in the thyroid gland in cases of exophthalmic goiter in which iodine was and was not administered.

Marine and Williams,[14] in 1908, published the results of a study of seventeen patients with exophthalmic goiter who had been treated with iodine preoperatively, and came to the conclusion that there was an increase in the colloid following iodinization. The study of glands from

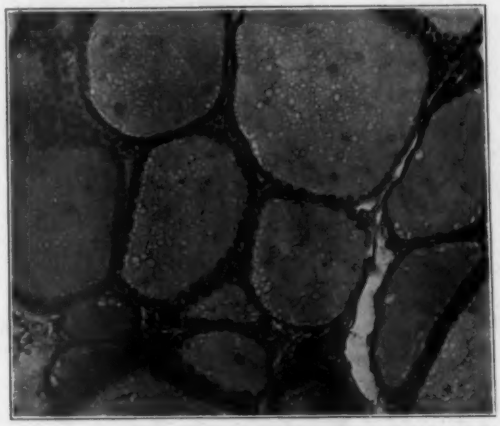

Fig. 4.—A thyroid gland (after the administration of iodine) in which colloid was graded 4, hypertrophy graded 1 and hyperplasia graded 1; × 120.

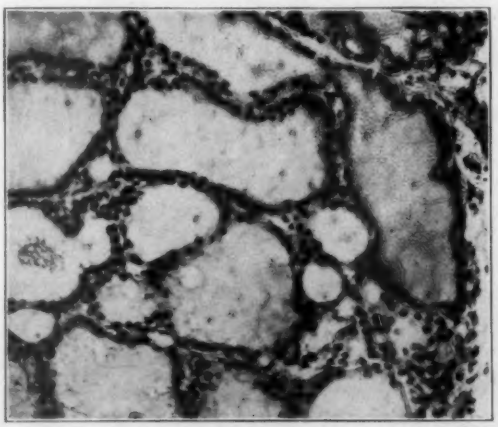

Fig. 5.—A thyroid gland (after the administration of iodine) in which colloid was graded 3 and hyperplasia and hypertrophy each graded 2; × 120.

patients was a small part of the work reported, which discussed fully the effect of iodine on the hyperplastic glands of dogs. Thyroid glands from dogs, sheep and other animals were studied. Hyperplasia was brought about by a removal of part of the gland. The presence of such

14. Marine, David; and Williams, W. W.: The Relation of Iodine to the Structure of the Thyroid Gland, Arch. Int. Med. **1**:349-384 (May) 1908.

hyperplasia and hypertrophy was recognized by Wagener [15] in 1884 and described clearly by Victor Horsley in 1896.[16] Welch,[17] in 1888, also mentioned the phenomenon and described Halsted's work on the subject. Halsted [18] mentioned, in addition, the part played by iodine in the prevention of hyperplasia. Horsley had previously found (1886) that, following partial removal of the thyroid gland from dogs, hyperplasia and hypertrophy occurred, with engorgement of the blood vessels and diminution of colloid. In one case the dog was killed 160 days after operation. The animal, a young female, had exercised the function of a parent and increased in weight and size during this period. Horsley [16] said: "The lobe of the gland that was left became hypertrophied so as to be four to five times its normal size. . . . Increase in the activity of the organ appeared therefore to cause a decrease in the consistence of the colloid and this was contrasted with the greater solidification of the acinal contents that occurred when the function of the gland was less active."

Oswald,[19] in 1902, called attention to the fact that the iodine content of goiters varies directly with the amount of colloid present. This was a step in advance, as Baumann who had discovered the presence of iodine had drawn the erroneous conclusion that there was always less iodine in goiters than in normal thyroid glands, which, Oswald points out, was a result of his dealing with glands that contained little colloid. Marine and, more recently, Cattell [20] concluded that the amount of colloid and iodine varied proportionately.

I found that in seventy-six of the total 100 glands studied, there were more marked changes (graded 4) in the colloid after the administration of iodine. In these the colloid was evenly distributed and distended practically all acini of different parts of a section. Twenty-two of the glands were graded 3; they showed slightly less colloid, there

15. Wagener: Ueber die Folgen der Extirpation der Schilddrüse nach Versuchen an Thieren, Wien med. Bl., 1884, nos. 25 and 30.

16. Horsley, Victor: A Discussion on the Pathology of Exophthalmic Goiter, Brit. M. J. **2**:895, 1896.

17. Welch, W. H.: Demonstrations of Pathological Anatomy. Microscopical Specimens of the Thyroid Gland After Partial Extirpation, M. News **3**:455, 1888.

18. Halsted, W. S.: Factors Which May Be Concerned in Causing Hypertrophy of the Thyroid Gland and the Effect of Excision of this Organ upon Other of the Ductless Glands, Tr. A. Am. Phys. **28**:127-135, 1913.

19. Oswald, A.: Die Chemie und Physiologie des Kropfes, Virchows Arch. f. path. Anat. **169**:444-479, 1902.

20. Cattell, R. B.: The Pathology of Exophthalmic Goiter. A Histological and Chemical Study of the Change Following Administration of Iodine (Lugol's Solution), Boston M. & S. J. **192**:989-996, 1925.

being areas in which the acini were full of colloid but also small areas in which it was almost absent. Colloid in the other two glands of the group was graded 2. In the 100 other glands (no iodine having been given) twelve were graded 4 as to colloid, fourteen were graded 3, twenty-six were graded 2 and forty-eight were graded 1.

In the cases in which iodine was given and in those in which it was not given, the amount of colloid increased as the amount of hyperplasia decreased, a point mentioned in 1908 by Marine and Williams as true in general for thyroid glands. As a check on the accuracy of the grading, the average grade of hyperplasia in each of the four grades of colloid was estimated in both types of gland. This also gives clearly the idea of the inverse ratio between the amount of colloid and the extent of hyperplasia. In the thirteen glands (without the administration of iodine) graded 4 for colloid, the average grade of hyperplasia was 1.53; in the fourteen glands graded 3, the average grade of hyperplasia was 1.55; in the twenty-six glands graded 2, the average grade of hyperplasia was 3.7, and in the forty-eight in which colloid was graded 1, the average grade of hyperplasia was 3.76. After the administration of iodine, seventy-six of the glands were graded 4 for colloid with an average grade of hyperplasia of 1.6, twenty-two were graded 3 with an average grade of hyperplasia of 1.9 and twenty were graded 2 with an average of grade 3 for hyperplasia.

Attention should be directed to the work of Giordano and Caylor with regard to the effect of ligation of the superior pole of the thyroid gland on the histologic appearance of the gland, before iodine was used and in the preoperative preparation of patients for partial lobectomy. "The most constant finding of the early period in the sections taken near the ligated areas was a tendency for the lumina of the follicles to be large and filled with colloid." Summarizing, it may be concluded that as the thyroid is iodinized the amount of colloid increases and the hyperplasia and hypertrophy decrease. A review of some of the experimental work in animals shows an interesting relationship between hyperplasia, colloid and iodine deficiency in this group. The investigations of Marine and Giordano and Caylor on the glands of human beings show the same anatomic picture with regard to colloid that I have noted.

CHANGE IN DEGREE OF HYPERPLASIA

The word hyperplasia is used here to describe a condition in the parenchyma of the gland in which the number of cells appeared to increase, although this was not proved. The hyperplasia noticeably decreases after the administration of iodine, which coincides with the relationship of colloid and hyperplasia (figs. 6 and 7). With the dis-

cussion of hyperplasia the question of mitosis arises, but since I noted the condition so infrequently it is not of significance here.

In forty-eight glands (without iodine) graded 4, hyperplasia was graded 3 in eighteen, in eighteen it was graded 2 and in sixteen it was graded 1. In fourteen glands, after the administration of iodine, hyperplasia was graded 3; in thirty-four it was graded 2 and in fifty-two it was graded 1. As will be shown when the grades for the various degrees of hypertrophy are given later, there is a direct relationship between hyperplasia and hypertrophy, while that between colloid and hyperplasia is indirect.

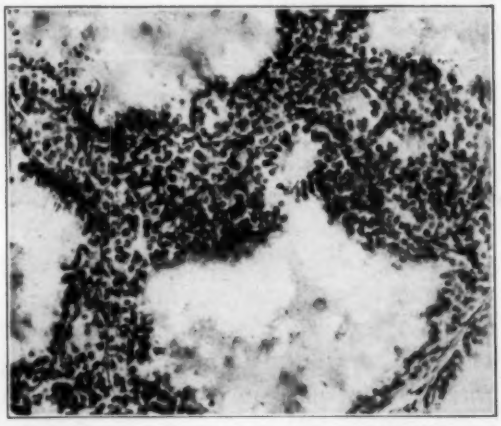

Fig. 6.—A thyroid gland in which colloid was graded 2 and hyperplasia and hypertrophy each graded 3 (no iodine was administered); × 120.

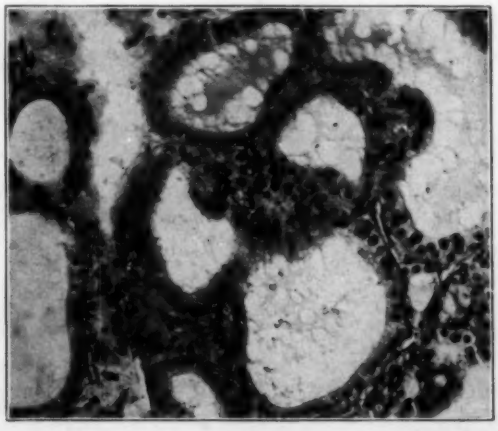

Fig. 7.—A thyroid gland (after the administration of iodine) in which colloid was graded 2 and hyperplasia and hypertrophy each graded 3; × 120.

Marine, in writing on the pathologic anatomy of exophthalmic goiter, stated that as the colloid accumulates in the gland during a regressive stage, the high columnar epithelium with its infoldings slowly returns to cuboidal. If the involution to a colloid type of gland is complete, the infoldings take on more of the appearance of small tufts of stroma jutting into the follicular lumen covered with the prevailing type of epithelium. Marine and Lenhart,[21] discussing the reversion taking place in the thyroid in cases of exophthalmic goiter not treated by iodine, described anatomic changes that cannot be differentiated from the change which takes place in the gland in exophthalmic goiter after treatment with iodine, except that after treatment with iodine there seems to be more of a tendency for the hyperplasia to disappear without leaving a trace of its presence in the form of the tufts already described.

Halsted, in 1896, predicted the foregoing anatomic changes in the goiters after iodine had been given, although he was discussing the anatomic changes which would take place during reversion of an exophthalmic gland to a normal anatomic state. "Change backward from hypertrophy to normal would be a simple matter; the shrinkage of the epithelium, the atrophy of the new if indeed they are new blood vessels and the formation of normal colloid, would accomplish the transition."

The experimental production of hyperplasia and hypertrophy by Horsley, Marine, Loeb and others[22] in the thyroid glands of dogs, guinea-pigs, monkeys, sheep and goats was uniformly successful. All agreed, with the exception of Loeb, that the administration of iodine would either prevent hyperplasia in these glands or cause it to decrease or disappear. Loeb found that the administration of iodine in guinea-pigs had no effect on the hyperplasia of the gland and concluded that there was a slight increase in the hypertrophy and hyperplasia in his animals after they had received iodine. Giordano and Caylor observed

21. Marine, David; and Lenhart, C. H.: The Colloid Glands (Goitres), Their Etiology and Physiological Significance, Bull. Johns Hopkins Hosp. **20**:131-139, 1909; The Pathological Anatomy of the Human Thyroid Gland, Arch. Int. Med. **7**:506-535 (April) 1911; Pathological Anatomy of Exophthalmic Goiter, ibid. **8**:265-316 (Sept.) 1911.

22. Loeb, Leo: Studies on Compensatory Hypertrophy of Thyroid Gland: IV. The Influence of Iodine on Hypertrophy of the Thyroid Gland, J. M. Research **41**:481-494, 1919-1920; Studies on Compensatory Hypertrophy of the Thyroid Gland: V. The Effect of the Administration of Thyroid, Thymus Gland and Tethelin and of a Meat Diet on the Hypertrophy of the Thyroid Gland in Guinea-Pigs, ibid. **42**:77-89, 1921. Loeb, Leo; and Kaplan, E. E.: Studies of Compensatory Hypertrophy of the Thyroid Gland: VI. The Effect of Feeding Anterior Lobe of the Pituitary Gland on the Hypertrophy of the Thyroid Gland in the Guinea-pig, J. M. Research **44**:557-578, 1924.

in the glands removed following preoperative ligation, an increase in the number of spriglike processes, which MacCallum has considered the remains of hyperplastic tufts, with a decrease of the amount of actual hyperplasia.

Marine suggested that the reason for the infolding that accompanies hyperplasia is mechanical, dependent on the increase in the number of cells, without a corresponding increase in the acinus. Marine and Lenhart, in 1911, called attention to the fact that these infoldings are less marked in nonencapsulated glands, as in fish.

The change taking place in the gland in exophthalmic goiter after iodine has been given is similar to that described by Marine during reversion in exophthalmic goiter and similar to what Halsted predicted would occur during reversion of a hyperplastic gland to normal. A

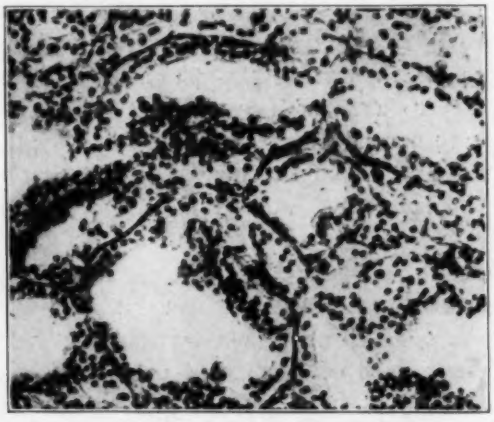

Fig. 8.—A thyroid gland in which colloid was graded 1 and hypertrophy and hyperplasia were each graded 4 (no iodine was administered); × 120.

review of some of the experimental work shows a close relationship between hypertrophy, hyperplasia, colloid formation and the ingestion of iodine, and the anatomic pictures, after the administration of iodine, are similar to those observed in this study. Again, in reviewing the work of Giordano and Caylor, a similar anatomic picture is noted. It is probable that, in the case of the ligated thyroid, much the same condition is produced as by removal of thyroid tissue, while the administration of iodine brings about a condition of the gland which is more nearly normal physiologically and anatomically.

CHANGE IN DEGREE OF HYPERTROPHY

I have considered that the extent and nature of the columnar epithelium provided an index of the degree of hypertrophy. The columnar epithelium also changed after the administration of iodine. It was not present in as large quantity. There was a marked increase in the amount

of cuboidal epithelium lining the acini (figs. 8 and 9), a certain variable percentage of which was low cuboidal, and some so flat as to lose even the characteristics of low cuboidal epithelium, the cells being low in proportion to their width at the base. In the cases in which iodine was given, the extent of columnar epithelium was never graded 4, whereas of the other 100 it was graded 4 in fourteen; it was graded 3 in twenty-four and thirty-six respectively, graded 2 in eighteen and twenty-eight respectively and graded 1 in fifty-eight and twenty-two respectively.

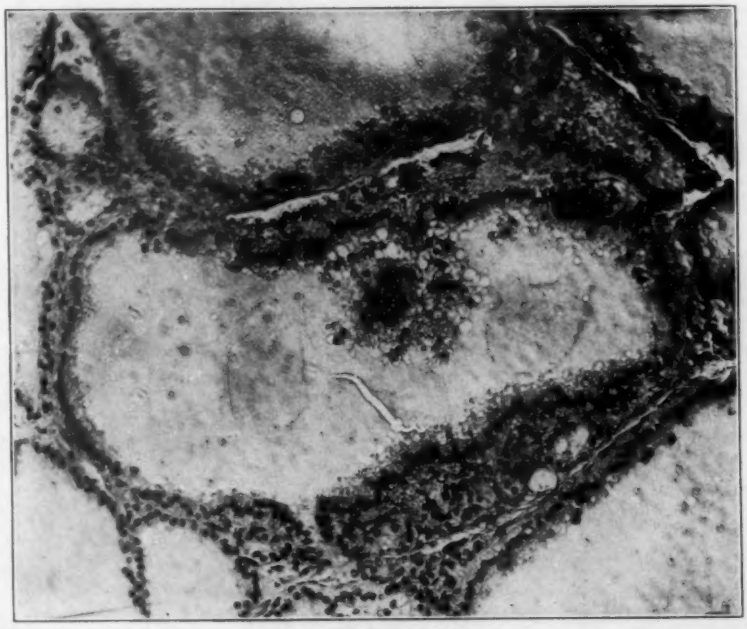

Fig. 9.—A thyroid gland (after the administration of iodine) showing active hyperplasia and also a large amount of colloid, suggesting that the appearance of colloid is the first change following iodinization; × 120.

The decrease observed in the amount of hypertrophy agrees with the conclusions of Marine and Williams in 1908, and of Cattell and Rienhoff [23] in recent papers which will be reviewed later.

It is interesting to note that in this histologic detail the results are similar to those obtained by Giordano and Caylor, in the work already quoted. Marine found a decrease in the hypertrophy combined with the hyperplasia in the experimentally produced hyperplasia of the thyroid of dogs.

23. Rienhoff, W. F.: The Historical Changes Brought About in Cases of Exophthalmic Goiter by the Administration of Iodine, Bull. Johns Hopkins Hosp. **37**:285-306, 1925.

CHANGES IN THE STROMA

Under the heading of changes in the stroma, I shall consider blood vessels, connective tissue and lymphocytic cells.

Marine, MacCallum and Wilson pointed out the increase in the amount of connective tissue in the thyroid in cases of exophthalmic goiter. It is easily recognized, and all observers agree regarding its presence.

In the present study there appeared to be less connective tissue relative to the amount of parenchymatous tissue and colloid, speaking quantitatively, after the administration of iodine (fig. 10). Whether this indicated that there were fewer connective tissue cells, was due to mechanical pressure or was simply a relative increase in the amount of

Fig. 10.—Typical thyroid gland after the administration of iodine: colloid distending acini, little hypertrophy and hyperplasia, cells cuboidal and flat, with occasional hyperplastic and hypertrophic areas sufficiently marked to justify its classification as unmistakably a hyperplastic gland; × 120.

colloid could not be ascertained from the sections examined. The histologic picture, however, suggested rather that it was a pressure phenomenon caused by the distention of the acini and consequent relative decrease in stroma generally. It is to be noted that the greatest amount of colloid is often locally associated with the least amount of columnar epithelium, and between such acini there is often little stroma. This suggests the operation of a mechanical factor to make the stroma appear less.

The lymphocytic areas present in the gland after the administration of iodine presented the same anatomic picture as when iodine was not given. They were present in small nodes or without organization. Apparently there was not any increase or decrease.

The blood vessels seemed smaller by comparison, although I could not be sure of this, as the change, if any, was so small as to require in the larger arteries exact comparison of the same blood vessel before and after the administration of iodine. Such comparison was impossible in this study, and would probably have been misleading even if practicable because of possible change in the gland not due to iodine. In the capillaries, however, there is probably a decrease in caliber, which, if present, would probably necessitate a smaller arterial supply or a lessened blood flow, amounting physiologically to the same thing.

Giordano and Caylor observed an increase in the amount of connective tissue in the areas adjacent to the ligated superior pole, where the changes described by them occurred. "In a few cases this change was so extensive as well to deserve the name given by Marine of 'cirrhosis of the thyroid gland.'" It is impossible to do other than surmise the reason for the increase in the connective tissue found by Giordano and Caylor. It seems logical to believe that all the changes are the result of diminution of the blood flow, lessening nutrition to the part of the gland supplied, and that the increased amount of connective tissue is evidence of degeneration. In the glands, however, after the administration of iodine, the whole pathologic process associated with exophthalmic goiter in the thyroid has been retarded and a type of gland produced which is probably as near the normal as the gland may become anatomically, considering the previous anatomic change, the presence of an adequate amount of iodine and the stimulation to which the gland is subjected.

Plummer described a small group of glands in 1913 which are of special interest at this point in the study. "The sequence (in exophthalmic goiter) is an intensive stimulation from some unknown source of the entire previously normal thyroid, diffuse hypertrophy, increased output of thyroxin, hyperthyroidization of the organism and, when the functional integrity of the epithelium is threatened, hyperplasia. In rare instances the stimulus may be of relatively low intensity for a considerable period causing hyperthyroidism without development of hypertrophy. There is a small group of patients having near normal or colloid glands and the clinical complex of exophthalmic goiter." I have not been able to find a previous description of this group, this being the first description noted in the literature.

Since, as I have shown, iodine brings about an increase in the amount of colloid, a decrease in the hypertrophy and hyperplasia, the small group of patients mentioned by Plummer should be enlarged. In this study the increase in the colloid seemed to be the most marked change produced by iodine, change in degree of hypertrophy the next and change in degree of hyperplasia third. This suggests the possibility, from an anatomic point of view, of the presence of a change in the

colloid with little or no hypertrophy in an exophthalmic condition, provided the stimulation of the thyroid is mild. This would probably be the condition at the onset of the disease for a time, the length of which there is no way of estimating. From the standpoint of pathologic diagnosis this is important, because the use of iodine should add to this group those cases in which the gland has progressed one step farther and is hypertrophic but not hyperplastic.

Recently several noteworthy papers have appeared in the literature, two of the earliest by Cattell and Rienhoff. Cattell's conclusions are that after the administration of iodine there is a decrease in vascularity, hyperplasia and hypertrophy, an increase in colloid and a decrease in the amount of connective tissue, that lymphocytic foci remain, as well as numerous scars, and that there is an increase in the iodine content of the gland. Rienhoff's conclusions are that there is an increase in the thyroid gland as a whole, a decrease in vascularity and probably in lymph flow through the gland, a large increase in the colloid deposited and contained within the thyroid, a change in the acini from lacelike ingrowths to round, even walled acini regular in size and shape and a change in the nuclei from large clear nuclei to a small irregular pyknotic type. He observed many mitotic figures before the use of iodine, and their absence after iodine had been given.

SUMMARY

There is an increase in colloid and a decrease in hypertrophy and hyperplasia in the thyroid gland after the administration of iodine. There is probably a decrease in the amount of connective tissue and in the size of the arteries and capillaries. Iodine does not have any effect on the number of lymphocytes present.

INTRATHORACIC GOITER *

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During recent years, many articles relating to pathologic lesions of the thyroid gland have appeared in the literature, but intrathoracic goiter has received scant attention. It is with the hope of contributing something to the solution of the various problems presented by this condition that I am offering this analysis of 100 cases of complete intrathoracic goiter, together with a review of the literature.

GENERAL REVIEW OF THE LITERATURE

Attention was first focused on this condition between the years 1912 and 1916, during which period an occasional article or case report was presented in the foreign literature. Since that time, articles have appeared from time to time in both American and foreign journals.

In 1914, Key [1] described two cases of intrathoracic goiter in which operation was performed by the Sauerbruch-Schoemaker technic (resection of part of the sternum). In 1917, Lahey [2] described the mechanism of the production of intrathoracic goiter and discussed diagnosis and treatment. In 1918, Lamson [3] reported a case of bilateral intrathoracic goiter, and described the management of the case. In 1919, Leiner [4] reported a case of true intrathoracic goiter with symptoms of thyrotoxicosis. As the goiter was small and there were no symptoms of pressure, medical treatment was instituted and relief from symptoms resulted. In 1920, Plenk [5] described and classified substernal goiters. and discussed their operative management, advising the splitting of the sternum. In 1920, Odermatt [6] reported a case of intratracheal struma in which operation was performed.

In 1920, Lahey [7] again discussed etiology, diagnosis and management in cases of intrathoracic goiter, considering them as of two types—

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* From the Cleveland Clinic.

1. Key, E.: Ein mit Erfolg operierter Fall von intrathorakaler Struma, Nord. med. Ark. **14**:1, 1914.

2. Lahey, F. H.: Intrathoracic Goiter, Boston M. & S. J. **176**:341, 1917.

3. Lamson, O. F.: Intrathoracic Goiter, Surg. Gynec. Obst. **27**:397, 1918.

4. Leiner, J. H.: Intrathoracic Goiter, New York Med. J. **110**:190, 1919.

5. Plenk, A.: Zur Sternumspaltung bei substernaler Struma, Deutsche Ztschr. f. Chir. **156**:378, 1920.

6. Odermatt, W.: Intratracheal Strumas, Deutsche Ztschr. f. Chir. **157**:279, 1920.

7. Lahey, F. H.: Diagnosis and Management of Intrathoracic Goiter, J. A. M. A. **75**:163, 1920.

incomplete and complete. In the incomplete type, the major portion of the thyroid is in the neck and is visible; and in the complete type, the major portion of the gland lies within the thorax, no part of the goiter being visible or palpable, except that in some cases the upper pole may be barely palpable above the presternal notch. In his discussion of surgical treatment, Lahey recommended the delivery of the thyroid as a whole into the neck rather than a piecemeal delivery with consequent hemorrhage.

In 1920, Rachford [8] presented a case of substernal goiter in which symptoms of pressure were present. Fifteen roentgen-ray treatments were given, and improvement resulted. In 1921, Brunner [9] gave a clinical picture of intrathoracic cystic accessory struma. In the case reported by him operation was not performed, but the patient died of paralysis of the heart following an attack of grip six years later, and the diagnosis of goiter was confirmed at autopsy. Brunner cited a similar case of Dittrich's.

In 1921, Lahey [10] again presented a number of case reports and described the treatment employed in each. In one case, the intrathoracic goiter was associated with hyperthyroidism. He stated that adenoma is the most frequent type of intrathoracic goiter. In order to prevent rupture of the pleura and hemorrhage, he recommended the placing of a pack in the cavity after the removal of the goiter.

In 1922, Terry [11] described the plunging and fixed types of intrathoracic goiter, classifying the symptoms according to interference with, or pressure on, the adjacent structures. He recommended that when division of the sternum is necessary longitudinal division be employed. In 1922, Seelig [12] reported a case in which cholelithiasis, intrathoracic goiter and hyperthyroidism were present.

Hertzler [13] and Crotti [14] have also discussed the diagnosis and management in cases of intrathoracic goiter, and articles by Wölfler,[15]

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8. Rachford, B. K.: Substernal Goiter with Pressure Symptoms, Am. J. M. Sc. **160**:410, 1920.

9. Brunner, H. C.: Intrathoracic Cystic Accessory Strumas, Beitr. z. klin. Chir. **122**:114, 1921.

10. Lahey, F. H.: Intrathoracic Goiter (Secondary Hyperthyroidism), S. Clin. N. Amer. **1**:641 (June) 1921.

11. Terry, W. I.: Intrathoracic Goiter, S. Clin. N. Amer. **2**:489 (April) 1922.

12. Seelig, M. G.: Cholelithiasis and Intrathoracic Goiter, S. Clin. N. Amer. **2**:1549 (Dec.) 1922.

13. Hertzler, A. E.: Diseases of the Thyroid Gland, St. Louis, C. V. Mosby Company, 1922.

14. Crotti, A.: Thyroid and Thymus, Philadelphia, Lea & Febiger, 1918, p. 140.

15. Wölfler, quoted by Plenk (footnote 5).

Kocher,[16] Monnier[17] and Perthes[18] are also of interest. In cases in which there is high stenosis Wölfler advised a primary tracheotomy, followed two weeks later by removal of the goiter. Kocher stated that exenteration may be advisable after resection of the sternum or ribs, and that, if necessary, this may be performed transpleurally. Perthes advised mediastinotomy according to the technic of Sauerbruch. Monnier reported one case in which the sternum was split and partial exenteration performed and called attention to the hemorrhage which may occur in this operation.

Molner[19] recommended the preoperative use of roentgen-ray therapy to reduce the size of the intrathoracic goiter. Judd[20] also discussed intrathoracic goiters: classification, symptoms and treatment. He emphasized the importance of the relationship of the goiter to vital structures, the need of freeing the upper pole first and the importance of avoiding manipulation outside the fibrous capsule.

In 1923, Haberer[21] reported a case of retrosternal struma associated with a diverticulum of the esophagus and a bleeding gastric ulcer. Strumectomy and excision of the diverticulum were performed, followed later by resection of the stomach. The ulcer was small, and the author thought that possibly healing had been prevented by the stasis in the venous circulation produced by the struma. He had frequently noticed stasis catarrh of the stomach when large strumas were present.

In 1924, in a discussion of the symptoms, diagnosis and treatment in intrathoracic goiter, Levin[22] recommended the transverse division of the sternohyoid and sternothyroid muscles as providing the best exposure.

In 1924, Hünermann[23] discussed diagnosis and treatment in intrathoracic goiter and also the frequency with which this condition has been seen in his own and in other clinics. He stated that the discrepancy in incidence is doubtless due to varied methods of classification.

In 1925, Grier[24] discussed the use of radiation in the treatment of patients who had intrathoracic goiter, stating that amelioration of

16. Kocher, T.: Text-book of Operative Surgery, London, Adam & Charles Black, 1903, p. 147.

17. Monnier, quoted by Hünermann: Arch. f. klin. Chir. **122**:789, 1923.

18. Perthes, quoted by Plenk (footnote 5).

19. Molner, A. L.: A Case of Retrosternal Goiter, Klin. Wchnschr. **1**:420, 1922.

20. Judd, E. S.: Intrathoracic Goiter, Internat. Clin. **1**:149, 1920.

21. Haberer: A Diverticulum of the Esophagus, a Retrosternal Goiter and a Bleeding Gastric Ulcer in the Same Patient, Arch. f. klin. Chir. **122**:789, 1923.

22. Levin, S.: Intrathoracic Goiter, J. Michigan M. Soc. **23**:208, 1924.

23. Hünermann, T.: Intrathoracic Goiter, Arch. f. klin. Chir. **128**:202, 1924.

24. Grier, G. W.: Is Irradiation a Satisfactory Treatment for Substernal Thyroid? Am. J. Röntgenol. **13**:327, 1925.

the symptoms and decrease in the size of the goiter follow the use of roentgen-ray therapy in cases of adenoma and of exophthalmic goiter, while this form of treatment has no effect on colloid or cystic goiters. He concluded that if the tumor can be removed without risk, a surgical procedure is the method of choice; but if considerable risk attends the operation, radiation is indicated.

In 1925, Noehren [25] discussed symptoms and treatment in intrathoracic goiter, and in 1926, Aleman [26] described two cases in which anterior mediastinotomy was performed.

CLASSIFICATION

Opinions differ greatly as to the correct grouping of intrathoracic goiters, some authors considering that only those tumors which lie entirely in the thorax should be classified as intrathoracic goiters, while others include also those in which only a portion of the goiter passes down into the thorax. A similar confusion attends the classification of substernal and subclavicular goiters. It is obvious that until a standard classification is adopted, it will be difficult to interpret correctly published reports of cases of intrathoracic goiter, as there will be discrepancies in the clinical picture, the incidence and the operative technic.

In the Cleveland Clinic, the following classification has been adopted:

I. Intrathoracic Goiter

(*a*) Complete

The greater part (four-fifths) of the goiter lies in the thorax and only the upper pole, or none of the glands is palpable above the sternum or clavicle.

(*b*) Incomplete

Only a part of the goiter extends into the thorax and at least one-half is palpable in the cervical region.

II. Substernal Goiter (Complete or Incomplete)

The entire goiter or a portion of it extends below the sternum.

III. Subclavicular Goiter (Complete or Incomplete)

The entire gland or a portion of it extends below the clavicle.

In figures 1 to 6 are shown schematic drawings illustrating the relative positions of the two lobes of the thyroid in some of our cases of intrathoracic goiter, and roentgenograms of other cases are given in figures 6, 7 and 8.

Terry has called attention to two other types of intrathoracic goiter, the "plunging" and the "fixed" types. The "plunging" intrathoracic goiter may be raised into the neck by coughing or by violent respiratory

25. Noehren, A. H.: Intrathoracic Goiter, Am. J. Surg. **39**:192, 1925.

26. Aleman, O.: Two Cases of Anterior Mediastinotomy for Intrathoracal Struma, Acta chir. Scandinav. **60**:135, 1926.

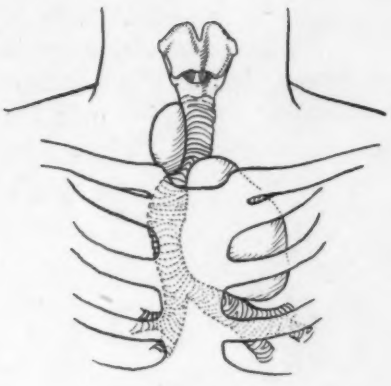

Figure 1

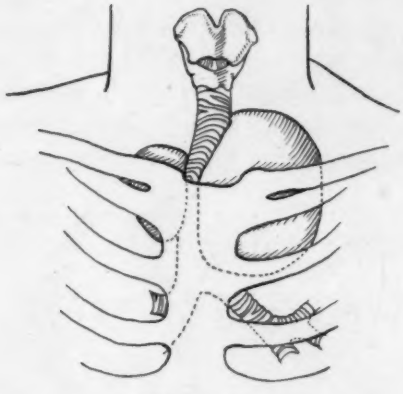

Figure 2

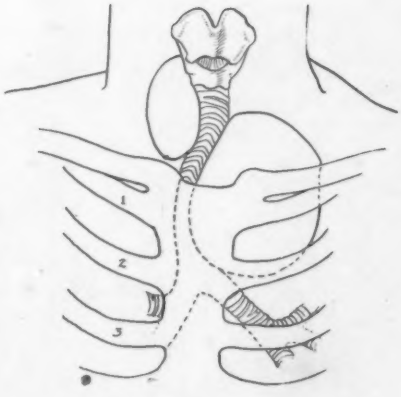

Figure 3

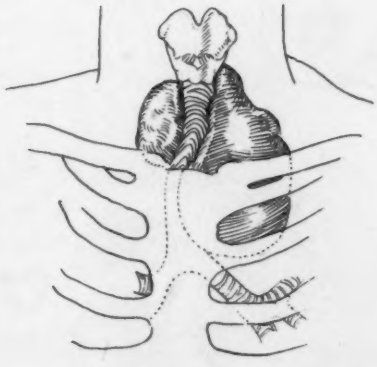

Figure 4

Fig. 1.—Schematic drawing showing left lobe of thyroid gland, almost entirely intrathoracic, with deviation of trachea toward the right.

Fig. 2.—Schematic drawing showing both lobes of thyroid gland partially intrathoracic and compression of trachea.

Fig. 3.—Schematic drawing showing right lobe of thyroid gland in normal position and large left lobe partly intrathoracic with compression and deviation of the trachea.

Fig. 4.—Schematic drawing showing both lobes of the thyroid gland enlarged and partially intrathoracic with marked compression and deviation of the trachea.

movements. Fluoroscopic examination frequently reveals a moderate extension of the goiter into the thorax, the goiter being entirely dislocated into the cervical region when the neck is extended. This is also often observed during operation. An interesting case of this type has been reported by Schwoerer;[27] on examination of his patient a complete intrathoracic goiter had been found, of which only the upper portion of the left lobe was visible on swallowing. There were

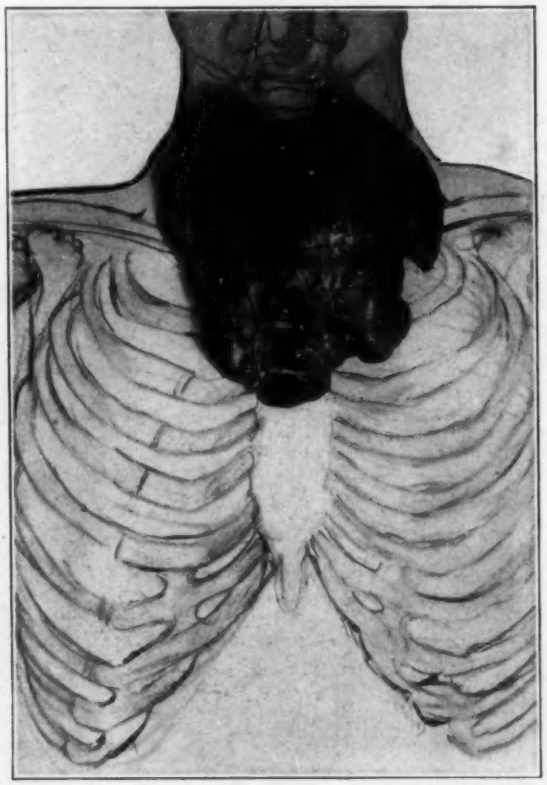

Fig. 5.—Schematic drawing showing the anatomic relations in a case of intrathoracic goiter.

also symptoms of hyperthyroidism. A few months after this examination, the patient tossed her head backward vigorously while shampooing her hair; she felt a violent pain in her throat; became faint and had symptoms of dyspnea. The physician discovered a tumor in the anterior side of the throat, between the jugular vein and the thyroid cartilage. This tumor increased in size, and when

27. Schwoerer, B.: Subkutane Strumaluxation, peri- und intrastrumöse Blutung, Beitr. z. klin. Chir. **131**:359, 1924.

the patient reached the hospital it was 12 cm. in length and 6 cm. in width. It was shaped like a sausage and lay in a transverse position. As palliative treatment did not relieve the condition, operation was performed the following morning. The tumor mass was found to be comprised of the left lobe of the thyroid. The lower veins of the left capsule were torn away and were drawn back toward the mediastinum in a great retrosternal hematoma. The capsule was intact, but it was tense and was blue-black. The parenchyma of the thyroid was completely destroyed and was filled with great clumps of coagulated

Fig. 6.—Roentgenogram showing the anteroposterior view of intrathoracic goiter posterior to trachea pushing the trachea forward and somewhat compressing it.

blood. The patient recovered well after the operation, and the symptoms of hyperthyroidism also disappeared. The "fixed" intrathoracic goiter remains in the thorax because of adhesions or because it is larger than the aperture between the thorax and the neck.

INCIDENCE

In analyzing reports on the incidence of intrathoracic goiter, the influence of variations in methods of classification is evident.

Von Eiselsberg found a substernal projection of one or both lobes in 50 per cent of his cases, partially intrathoracic goiters in 5 per

cent and totally intrathoracic goiters without a cervical portion in 1 per cent. Crotti reported that from 25 to 35 per cent of all the goiters in his cases and in those reported by other observers lay deep in the upper thorax, while from 15 to 18 per cent were partially intrathoracic. Hertzler reported 0.25 per cent as the incidence of the latter type. Levin reported that 20 per cent of the goiters which he had seen were deep-seated; 3 per cent were deep enough to be called intrathoracic. In Leiner's series of cases of goiter, from 6 to 7 per cent were intrathoracic. According to Terry's figures, in from 7 to 10 per cent of the goiters in his series a considerable portion of the gland lay in

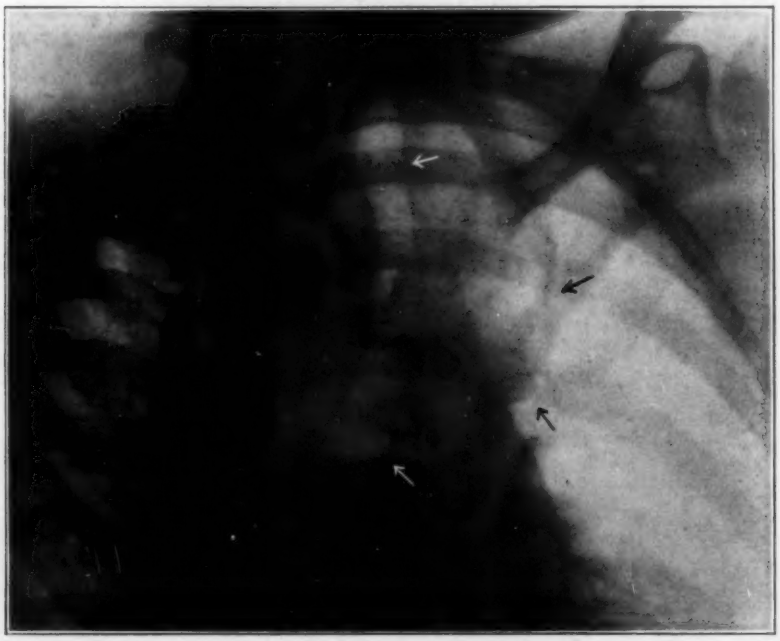

Fig. 7.—Lateral view of figure 6.

the thorax. Noehren stated that in from 7 to 18 per cent of his cases the goiter was intrathoracic.

Czermak [28] reported that of the 1,473 cases of goiter seen in the Innsbruck Clinic from 1912 to 1920, the goiter was intrathoracic in 487, or 32 per cent. Among these cases, the left lobe was retrosternal in 251 cases, or 51 per cent; the right lobe was retrosternal in 148 cases, or 41 per cent, and the right and left lobes were retrosternal in 59 cases, or 12 per cent. Reinbach [29] reported 31 cases of intra-

28. Czermak, quoted by Hünermann (footnote 23).

29. Reinbach, quoted by Hünermann (footnote 23).

thoracic goiter among 162 cases of goiter, an incidence of 19 per cent; Closs [30] reported 10 cases among 106 cases of goiter, or 9 per cent; Kocher stated that in 10 per cent of his cases the goiters were intrathoracic. Monnier found 114 cases of substernal goiter and 17 of intrathoracic goiter in a total series of 670 cases. Of the latter, the right lobe was in the thorax in 47 cases, the left lobe in 62 cases and the isthmus in 5 cases. Jackson reported an incidence of 542 substernal goiters, 13.5 per cent, and 25 intrathoracic goiters, 0.6 per cent, among 4,006 thyroidectomies performed at the Mayo Clinic for simple colloid and adenomatous goiter.

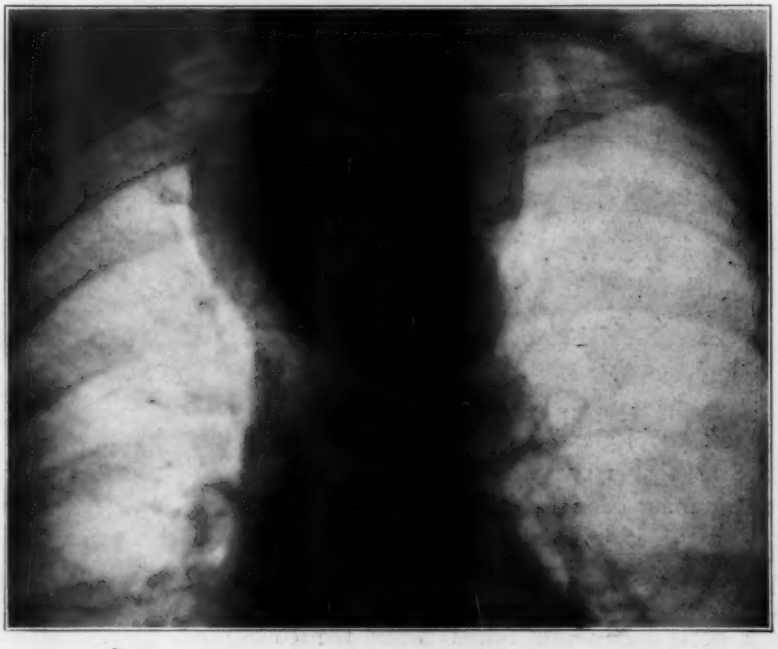

Fig. 8.—Roentgenogram of large intrathoracic goiter showing displacement of trachea to the right.

A comparison of these figures shows a variation in the incidence of from 1 to 18 per cent. In our own series, from 1 to 2 per cent of all cases may be classified as completely intrathoracic, while approximately 10 per cent have been of the incomplete type.

Age.—Intrathoracic goiter is rarely seen in children, and its incidence increases with age up to the age of 60 years. This increasing incidence is readily understood when it is realized that a goiter may occupy the cervical position for years before descending into the

30. Closs, quoted by Hünermann (footnote 23).

thorax; and that its descent may be incomplete until, because of gradual growth or because of hemorrhage into the intrathoracic portion, no portion of the growth can pass into the cervical region. When an intrathoracic goiter is present in a child, it is usually the result of an increase of aberrant thyroid tissue derived from accessory thyroid tissue carried into the mediastinum with the aortic portion of the thyroglossal duct. The age incidence in the series here reported, (table 1) shows an identical incidence at the two extremes of life, and the maximum incidence in the sixth decade.

Sex.—In our series, the incidence of intrathoracic goiter in women, 76 per cent, was markedly greater than in men, in whom it was only 24 per cent. These percentages correspond fairly closely to those for the sex incidence in our cases of hyperthyroidism and simple goiter.

TABLE 1.—*Age Incidence in Cases of Intrathoracic Goiter*

Age	Percentage
Under 20 years	5
20–30	6
30–40	15
40–50	22
50–60	27
60–70	20
70–80	5

ETIOLOGY

The thyroid gland is a median extension downward from the same anlage as that from which the tongue is derived, the thyroglossal duct becoming eliminated in the process of development. This downward growth is joined by cells coming from the postbranchial bodies, which later fuse and unite with it. In its final form, it consists of two lateral lobes joined by the isthmus. Small, detached portions of thyroid tissue occasionally are found along the course of the thyroglossal duct, and are called accessory thyroid glands.

The aortic portion of the thyroglossal duct may also carry accessory glands into the mediastinum, and if these become enlarged, an intrathoracic goiter results; if a cervical thyroid gland becomes enlarged later, an intrathoracic goiter may result, the following factors favoring its formation: (1) the anatomic arrangement of the muscles of the neck and (2) deglutition.

The sternothyroid muscle is attached to the posterior surface of the sternum and thus affords a smooth surface for the gland to slip over in entering the thorax, and because of the resistance offered by the anterior group of muscles in the neck, descent into the thorax becomes the path of least resistance. Posterior growth is limited by

the trachea, and lateral growth by the scalenus and sternomastoid muscles. Deglutition also tends to favor the downward growth of the tumor.

After the goiter—which in these cases is usually a colloid adenoma or a cyst—passes into the thorax, it may gradually increase in size, or, in rare cases, increase suddenly because of a hemorrhage into the cyst, the goiter becoming so large that it is unable to pass back through the aperture into the cervical region; it thus becomes fixed in the thorax. Terry also mentions the influence of gravity and the dragging effect of inspiration as factors in the etiology of intrathoracic goiter.

Fig. 9.—Photograph of patient with intrathoracic goiter showing engorgement of veins over chest.

SYMPTOMS

The symptoms of intrathoracic goiter may be divided into two groups: the subjective and the objective. They may be classified also according to the changes in the respiration and circulation and the alterations in adjacent structures which are produced by pressure.

The most important subjective symptoms are dyspnea, hoarseness, coughing, change in voice, stridor, dysphagia and symptoms of hyperthyroidism.

The dyspnea is usually continuous and is frequently associated with an inspiratory stridor. It was present in 66 per cent of the cases in our series. Because of this symptom a mistaken diagnosis of

asthma is sometimes made, as had happened in four of these cases. Choking occurred in 30 per cent, being more pronounced when the patient was in the recumbent position, because of the resultant increased pressure on the trachea. Dyspnea and choking are usually more pronounced when the goiter is in the median line and presses directly on the trachea.

Dysphagia, due to pressure, was present in some degree in 24 per cent of the cases. In seven cases this symptom was marked and was constantly increasing in severity, while in the other cases it was only moderate and intermittent.

Hoarseness and change in voice were present in 25 per cent of the cases. The onset of these symptoms had usually been insidious, and the symptoms were more pronounced in cold, damp weather and in the morning. In some cases, the voice seemed more impaired when patients were in the recumbent position, and the hoarseness tended to clear up during the day.

A few patients complained of coughing. This symptom is due either to irritation of the trachea by pressure or to irritation of the recurrent laryngeal nerves.

A moderate degree of stridulous breathing was present in 7 per cent of the cases, the onset of this symptom having been gradual. It was marked in two cases, in one of which bilateral abductor paralysis was present.

Headache, usually temporal and occipital, was present in 57 per cent of the cases.

Some symptoms of hyperthyroidism were present in many of the cases in this series. Although the complete clinical picture of the disease was not present, a sufficient number of the typical symptoms were observed to justify their classification as cases of hyperthyroidism. Tachycardia was present in 53 per cent of the cases, the rapid action of the heart having been noticed by the patient. In 27 per cent the pulse rate was above 130; in 12 per cent, between 120 and 130; and in the remainder, between 90 and 110. Nervousness was present to some degree in 61 per cent; in 27 per cent this symptom was very noticeable, in the others it was mild or present only at intervals. A loss of weight had been noted in 43 per cent of the cases, the loss averaging between 8 and 14 pounds (3.6 and 6.4 kg.) In 37 per cent a considerable degree of tremor was present, this symptom having been observed by the patient in the majority of the cases, often because of the resultant difficulty in writing. Exophthalmos occurred in 8 per cent of the cases. No cases of unilateral exophthalmos were observed, but unequal exophthalmos was noted in some cases. The basal metabolic rate was not determined in all the cases in which the symptoms of hyperthyroidism were observed, but in those in which estimations were made, the average rate was + 32 per cent.

The foregoing figures demonstrate that the absence of a palpable thyroid gland does not rule out the possibility of hyperthyroidism. Therefore when symptoms of hyperthyroidism are present and a gland cannot be palpated, a roentgenogram of the chest should be made to determine whether or not an intrathoracic goiter is present. In such a case, special care should be taken to avoid a mistaken diagnosis of neurocirculatory asthenia. In one of our cases a thyroidectomy had been performed some time before. The basal metabolic rate at the time of examination was + 57 per cent. An operation was performed

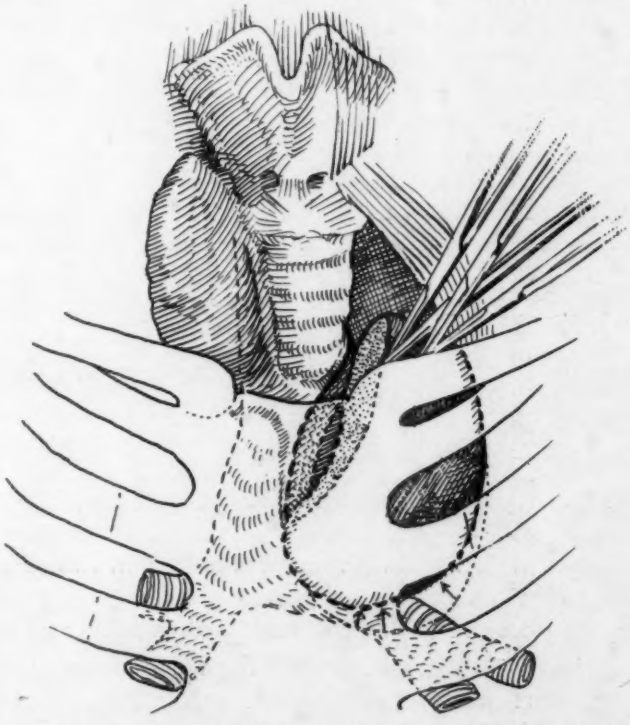

Fig. 10.—Schematic drawing showing technic of mobilization of the gland.

and a large intrathoracic goiter was removed. One month later, the basal metabolic rate had dropped to + 11 per cent.

In 13 per cent of the cases, there was evidence of preoperative paralysis of the recurrent laryngeal nerves; in 12 per cent, the left abductor was paralyzed, and in one case there was a bilateral abductor paralysis. Adductor paralysis has not been observed in any of the cases in this series. Because of the gradual involvement of the recurrent nerve, a tracheotomy has not been required in any case; this might have been necessary if the nerve had suddenly become involved. The more frequent involvement of the left nerve is difficult

to explain. The difference in the anatomic position of the recurrent nerves may have some bearing on this question. When one recalls that the left nerve springs from the vagus as it crosses the aortic arch, and, after passing around the arch, passes upward in the superior mediastinum between the trachea and esophagus, reaching the neck through the tracheo-esophageal groove, it would seem that its longer course might cause it to be more subject to trauma than is the shorter right nerve.

As the result of pressure on adjacent vessels, obstruction of the superior vena cava may occur, causing the venous blood to return by collateral channels and the vessels of the chest to become enlarged, engorged and prominent. In some cases the jugular veins are much distended, and extreme distention of the veins on the anteriolateral portion of the chest and abdomen becomes evident. The lips and face may also become cyanosed.

TABLE 2.—*Duration of Symptoms of Intrathoracic Goiter*

Duration	Cases
6 months–1 year	19
1 year–5 years	22
5–10 years	20
10–20 years	21
20–30 years	8
30–40 years	5
40–50 years	2
Over 60 years	30

Dittrich has reported a difference in the width of the pupils in cases of intrathoracic goiter, presumably caused by pressure on the sympathetic nerves. This phenomenon was present in two of our cases.

Inequality of the radial pulse, due to pressure on the subclavian artery, may also occur, but this was not observed in any of our cases.

Duration of Symptoms.—In determining the duration of the symptoms, every effort was made to secure accurate information, with the results given in table 2.

It is evident that among these cases are some in which the patients had had symptoms as long as they could remember.

DIAGNOSIS

There are several conditions the differential diagnosis of which should be borne in mind in any case in which the presence of an intrathoracic goiter is suspected, namely, Hodgkin's disease, mediastinal tumor, asthma, tuberculosis, mediastinitis, aneurysm of the aorta, persistent thymus, abscess of the lung and pneumonia.

As mentioned previously, four of the patients in this series had been treated for asthma as the result of a mistaken diagnosis. A

roentgenogram would have revealed the real cause of the trouble in these cases, but, owing to the fact that no toxic symptoms were present and only mild symptoms of pressure, a roentgen-ray examination was not made.

Hodgkin's disease can usually be ruled out by a careful history and examination for multiglandular enlargements, and the clinical diagnosis may be substantiated by biopsy.

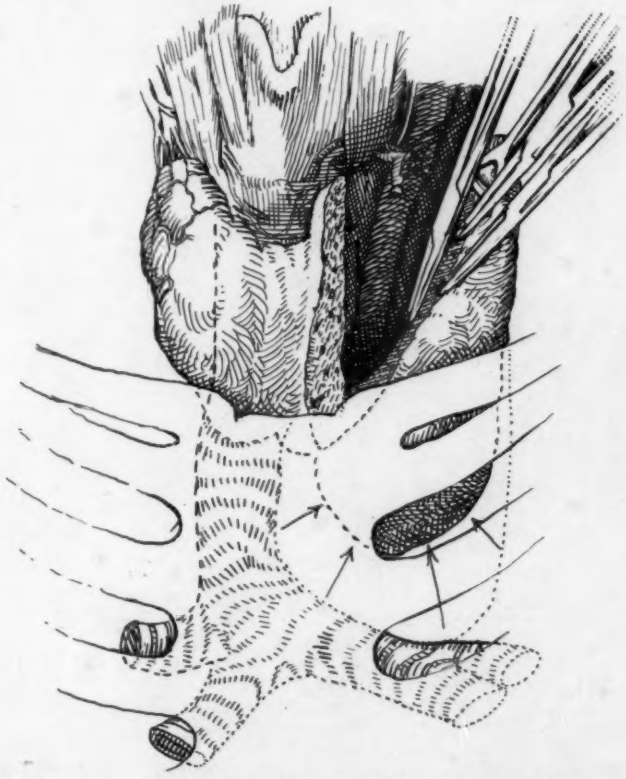

Fig. 11.—Schematic drawing showing technic of mobilization of the gland.

A persistent thymus usually occurs in a child. A careful history and roentgen-ray examination will usually rule out this condition. The possibility of a mediastinal tumor can also be ruled out by roentgen-ray examination. It may be difficult to differentiate between intrathoracic goiter and aortic aneurysm, but a careful history, a Wassermann test and roentgen-ray studies will establish the diagnosis.

The diagnosis of abscess of the lung and of pneumonia is easily established by the history, the physical signs and roentgen-ray examination. An esophageal diverticulum can be diagnosed by the history and by means of a barium meal, the roentgenogram revealing a dilated pouch connected with the esophagus.

Roentgen-Ray Examination.—The roentgen-ray examination should include stereoscopic roentgenograms in the anteroposterior and oblique positions; a fluoroscopic examination is also of value in differentiating between an intrathoracic goiter and an aortic aneurysm. A distinct angle is usually present between the aortic shadow and that of the intrathoracic goiter, a point which has been brought out by Crotti; this angle changes during inspiration and deglutition because of the ascent and descent of the goiter. This is an important observation in establishing the differential diagnosis, as is also a deviation or a deformity of the trachea.

PATHOLOGY

In the majority of cases of intrathoracic goiter, a colloid adenoma is present. A complete intrathoracic goiter is rarely found to be a hyperplastic gland. In this series, the pathologic reports showed the following conditions: fetal adenoma, sixteen cases; cystic colloid adenoma, twenty-seven cases; colloid adenoma, thirty-three cases; colloid goiter, twenty-one cases; and hyperplasia, three cases.

Fig. 12.—Complete mobilization of intrathoracic lobe.

In the majority of the cases in the series—69 per cent—the goiter was on the left side; it was on the right side in 35 per cent. In 6 per cent, it was bilateral.

TREATMENT

Surgical intervention alone is of avail in the treatment of patients with intrathoracic goiter. If the operation is performed at an early stage, when the tumor can easily be delivered into the neck, it is a safe procedure. The surgical mortality in the cases in this series has been only 1 per cent. A transverse division of the sternothyroid and sternohyoid muscles is rarely necessary. Evacuation of the contents of an intrathoracic goiter by morcellation is attended by hemorrhage, and should be avoided.

Technic.—After securing an adequate exposure, which in some cases necessitates a transverse division of the prethyroid muscles, the

upper pole of the gland is first freed from the trachea, to facilitate mobilization of the goiter, and the superior thyroid vessels are clamped and ligated. The thyroid is then freed downward from the trachea, care being taken to point the hemostats outward in order to avoid injury to the recurrent nerves. This dissection is continued until the entire upper pole is mobilized. The bleeding points are then ligated before an attempt is made to deliver the intrathoracic portion of the

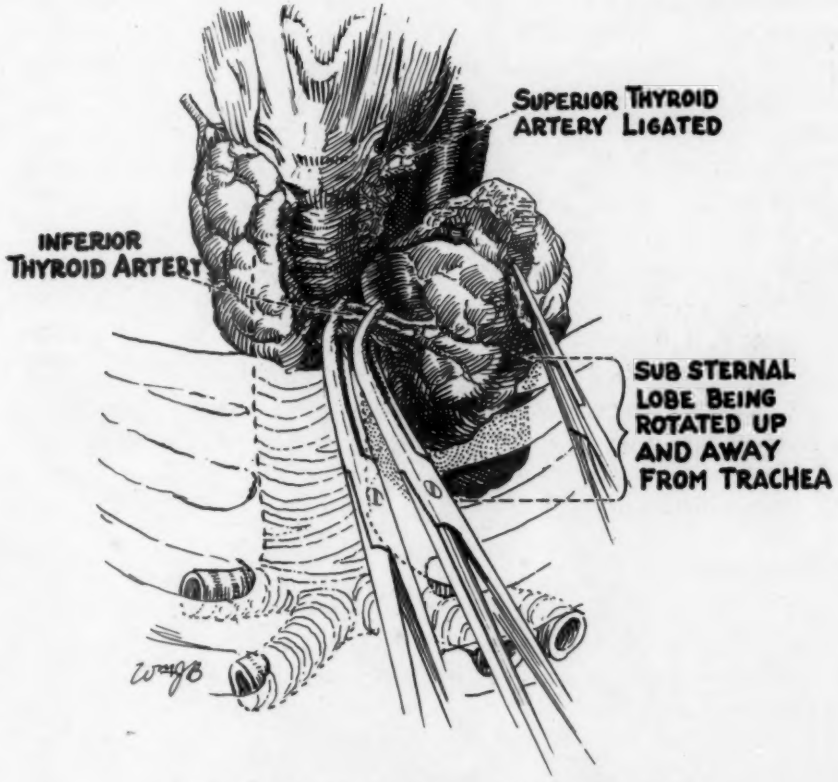

Fig. 13.—Location of inferior thyroid artery.

goiter. In this way the field is kept clean, and there would be no obstruction by hemostats should an emergency arise.

After the cervical portion of the gland has been completely mobilized, the finger can be passed down about the tumor, care being taken to avoid getting outside its fibrous capsule, and the tumor can be delivered into the neck. It is surprising how mobile the goiter becomes after the upper pole of the gland is freed from the trachea. It must be remembered always that the tumor is in close proximity to important structures and that the greatest caution must be used in delivering it.

The lower pole is then ligated. Ordinarily, arterial circulation enters the lower pole through the inferior thyroid artery, which communicates with the gland halfway between the poles and remains in the same location regardless of the position occupied by the goiter. After adequate hemostasis has been secured, a tape should be placed in the cavity to prevent rupture of the pleura or oozing into the mediastinum, and the incision is held open with acriflavine gauze. The tape should be removed at the end of twenty-four hours. A catheter can then be placed in the cavity in order to remove the serum by aspiration; the muscles can be reapproximated and the incision closed with clips, thus allowing the catheter to emerge through the center of the incision.

SUMMARY

1. Complete intrathoracic goiter is a relatively uncommon condition, the incomplete type being more frequently observed.

2. In cases in which the presence of an intrathoracic goiter is suspected, roentgen-ray examination should be made to rule out other conditions which may produce similar symptoms. In cases in which symptoms of hyperthyroidism are present and the thyroid gland is not palpable, roentgen-ray examination is indicated.

3. Surgical treatment alone can relieve the symptoms of intrathoracic goiter, and early operation is urgently advised. The surgical mortality can be kept to a minimum by careful management of the patient and by the avoidance of hemorrhage and of injury to adjacent structures.

PNEUMOCEPHALUS OF BACTERIAL ORIGIN *

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BALTIMORE

Intracranial air occurring during life may arise from two possible sources: (1) it may be forced through a break in the cranial bony and meningeal coverings overlying the air spaces, or (2) it may be a product of microbic origin. In a recent article of mine [1] the various aspects of pneumocephalus were considered at length, but my knowledge of this condition was then restricted to the first variety, in which the air was forced through an opening to the exterior. A case was presented, however, in which air was roentgenologically demonstrated in a cranial abscess, but the source of the air could not be absolutely determined. Although the air of bacterial origin was then considered a possibility, it was concluded, for reasons none too convincing when reviewed in retrospect, that more probably the air had entered through a break in the dura which was known to be present and through which pus was discharged intermittently when the dura was elevated. Unfortunately, the bacteriologic proof of the character of the organism was lacking.

At the time of the first publication I was not able to find in the literature any report of a case in which intracranial air of microbic origin occurred during life. This note is essentially a supplement to the first article. It presents a recent example of intracranial air arising from bacteria and assembles from the literature the reports of three other cases which escaped my notice at that time.

REPORT OF AUTHOR'S CASE

History.—A boy, aged 6, was ready to be discharged from the hospital one week after a mastoid operation (performed a week previously) when fulminating signs of intracranial pressure suddenly developed. Except that there had been intermittent discharge from both ears for the past four years, his past history was not significant. Three weeks before his admission to the Johns Hopkins Hospital, the discharge reappeared in the right ear. One week later, the soft tissues back of the right ear became swollen. This swelling gradually increased and became progressively more painful. Fever and chills had been present during the week before admission. When the mastoid operation was performed by Dr. Snelling, the dura was exposed; it was covered by granulation tissue, but there seemed to be no evidence of perforation. One week later, the patient complained of severe headache, and during the day he vomited several times. The pulse rate changed from 120 to 64 in less than twenty-four hours. There was marked papilledema in both fundi; the temperature remained unchanged and normal. An abscess in the temporal lobe was suspected because of the underlying mastoid infection.

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* From the Department of Surgery, Johns Hopkins University.

1. Dandy, W. E.: Pneumocephalus, Arch. Surg. **12**:949 (May) 1926.

Treatment.—Through a perforator opening beneath the temporal muscle, an abscess was immediately encountered by a puncture with a ventricular needle. An ounce or more of foul-smelling pus escaped. A week later intracranial pressure had returned, and again it was necessary to tap the abscess. Many bubbles of gas were then seen to spurt through the pus in the needle. A roentgenogram revealed a large round shadow of air in the temporal lobe. The intracranial pressure then returned so quickly that it was necessary to evacuate the abscess every two days and finally every day. The amount of gas became greater with each tapping, and the amount of pus both relatively and absolutely less (the intervals of time, of course, were growing shorter). As the infection was gaining the upper hand under intermittent tappings, a small rubber tube was inserted into the abscess cavity. Continuous drainage continued for five days after which the tube was withdrawn and a protective wick inserted. Drainage ceased a few days later. Six weeks after the abscess was first tapped, the roentgenogram showed no shadow of air, and a week later the patient was discharged as well.

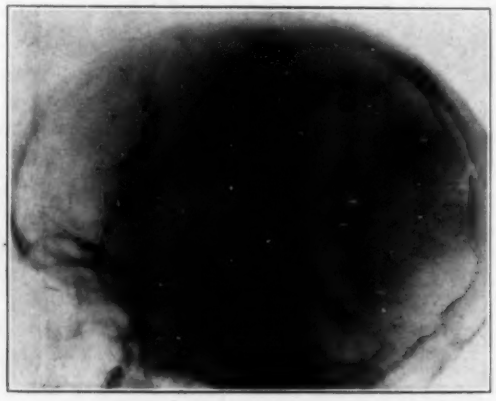

Fig. 1.—Roentgenogram (lateral view) showing collection of air (of bacterial origin) in an abscess of the temporal lobe.

One year later, the patient was still well in every respect. He had never had contralateral motor or sensory changes and no convulsions. The only symptoms at any time during his illness were those of intracranial pressure. Cultures were completely studied by Dr. Amoss in the bacteriological division of the medical clinic, but the organism which produced the gas could not be identified. He reported a heavy growth of gram-negative bacilli; dextrose and maltose fermented with production of gas. The organism was non-motile, non-spore-bearing and did not grow aerobically. Clearly, it was not *Bacillus aerogenes-capsulatus* of Welch. *Streptococcus viridans* also grew from the cultures of the abscess.

REVIEW OF THE LITERATURE

As mentioned before, I had been unable to find reports of similar cases when my article on pneumocephalus was published. Reports of three cases have since been found, one reported by Bier [2] and two by

2. Bier: Anaërobe Wundinfektion, Beitr. z. klin. Chir. **101**:271, 1926.

Rychlik.[3] All followed wounds of the head. Bier's patient died five days after a severe compound wound of the vault of the skull. Bubbles of gas were seen exuding with pieces of necrotic brain tissue. Necropsy was performed half an hour after death, but no mention was made of the cerebral abscess. Purulent meningitis was doubtless the cause of death. Although cultures were not made, Aschoff, who conducted the autopsy, considered the organism to be *Bacillus aerogenes-capsulatus*. Roentgenograms of the skull were not made.

Rychlik's cases were much more impressive. His first patient was only slightly injured by fragments of grenade. Consciousness was not lost, but on the following day he was sent to the hospital. On the third

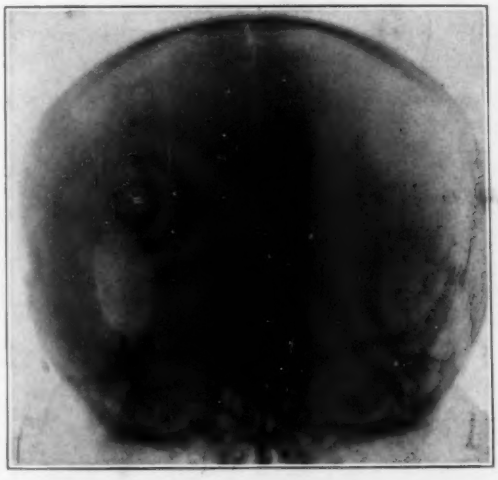

Fig. 2.—Roentgenogram showing collection of air (same case) in anteroposterior view.

day his temperature rose to 39 C. (102.2 F.), but the cause was first suspected on the fifth day, when headaches developed; as they were not severe, however, it seemed possible to explain them on the basis of his high fever. On the sixth day the left side became paralyzed. Bilateral papilledema was also present. An abscess was found in the frontal lobe, and the opening was enlarged with a finger. A second, smaller abscess in the temporal lobe was detected by the finger. The abscess drained several weeks. The patient was cured. From the cultures of the abscess the gas bacillus (B. welchii) was grown in pure culture. Apparently animals were not injected with cultures of this organism. Roentgenograms were not taken.

3. Rychlik, E.: Gasabszess des Gehirns, München. med. Wchnschr. **63**:1713, 1916.

As an appendix to this article, Rychlik adds a brief note of a second similar case. Two days after being injured by a grenade splinter, the patient developed severe headache and a temperature of 39 C. A frontal abscess was drained, and the patient recovered. Gas bacilli were grown in pure culture; no inoculations were made, nor were roentgenograms taken.

Probably the most surprising fact which has appeared from a study of these aerogenic infections is the low mortality under proper treatment; and in two of them (Rychlik's cases) the organism is the dreaded *Bacillus aerogenes-capsulatus* of Welch. The evidence is too meager to draw any conclusions about the outcome of Bier's case; in fact, the evidence presented is not sufficient to indicate that the air was of bac-

Fig. 3.—Photograph showing healed wound after drainage of air containing abscess (of bacterial origin).

terial origin. It may well have been forced through a bony defect of a frontal air sinus.

Although the organism in my case must remain unidentified, careful studies have eliminated the gas bacillus. Were it not for the fact that the organism has been shown to be gram-negative and non-spore-bearing, it might well have passed as a gas bacillus. The clinical behavior is not unlike that in Rychlik's case, in spite of the fact that the organisms may be different.

It seems incredible that the gas bacillus (of Welch), which causes such havoc when attacking other parts of the body, should be so innocuous in the brain. In my case there were never signs of illness other than those of intracranial pressure. On one occasion the patient's temperature rose to 102.6 F. (probably an index of pressure), but with

the exception of this brief elevation, the temperature ran at a fairly uniform level around 99 to 99.5 F. As soon as the intracranial pressure was relieved, he was playful and gave no impression of being sick, and in this respect both of Rychlik's cases are essentially the same. There can be no doubt that without drainage of the abscess all these patients would have died. Although I have been treating patients who have cerebral abscesses by simply evacuating the abscess instead of by continuous drainage, it was necessary in this case to resort to continuous drainage, for the rate of production of gas was soon overwhelming.

I have also been impressed with the failure of these infections to spread, as they are wont to do in other regions of the body. On the contrary, all have been isolated and have become well walled off. Rychlik mentions a second small abscess contiguous to the main abscess, but it drained satisfactorily through the common portal of exit.

Multiple gas abscesses of the brain have frequently been described in postmortem specimens. There has been no clinical proof, however, to indicate that these conditions have been of antemortem origin. In fact, it is well known that after death gas-forming bacilli take on new and unbridled growth, and this knowledge has caused the impression to prevail that these abscesses are all of postmortem origin. At least it remains to be proved that they are of antemortem formation.

SUMMARY

1. A case of pneumocephalus of microbic origin is reported. Two and possibly three other cases have been collected from the literature.

2. In three of these cases the organisms had formed cerebral abscesses. Though two were presumably caused by *Bacillus aerogenes-capsulatus* of Welch, they were isolated and well walled off. In my case the organism was not the bacillus of Welch. Though its characteristics have been carefully studied, its exact identity remains obscure.

3. In these cases there were almost no systemic symptoms due to the organism. The symptoms and signs were almost extensively those of intracranial pressure.

4. All of the patients were cured by continuous drainage.

INJECTION OF ABSOLUTE ALCOHOL IN THE TREATMENT OF HYPERTHYROIDISM *

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Experimental observations made by one of us (H. B. B.) [1] on the effect of the injection of absolute alcohol into the thyroid gland showed a local coagulation necrosis, the extent of which varied directly with the amount of alcohol injected. No general effect was observed. The experiments warranted the conclusion that the injection of absolute alcohol in suitable quantity in cases of disease of the thyroid is a safe and legitimate method. Following this conclusion, we have used this method of treatment in severe hyperthyroidism, and in this paper we report the results.

The use of multiple more or less minor operative procedures in preparation for subtotal thyroidectomy in severe cases of hyperthyroidism is well recognized. Though the use of compound solution of iodine as advocated by Plummer [2] has made it possible to convert many cases of exophthalmic goiter from poor risks to the class of fair risks or good risks, there remains a group of patients who do not respond sufficiently to medication to be satisfactory risks for subtotal thyroidectomy. In addition to these cases of exophthalmic goiter, there are cases of adenomatous goiter with marked hyperthyroidism and cardiac damage in which multiple procedures must be used in order to produce fair operative risks for eventual subtotal thyroidectomy. Any procedure which promises benefit and can be carried out with little risk to the patient is worthy of trial in these cases. Porter [3] and Crile [4] have emphasized the importance of the use of multiple procedure in the preparation of these patients for thyroidectomy. It is admitted that erring on the side of safety is the only practice that will prevent a high mortality in these types of cases. The minor procedures in common use

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1. Barker, H. B.: The Injection of Absolute Alcohol into the Thyroid Gland, Arch. Surg. **2**:180 (Aug.) 1925.

2. Plummer, H. S.: Results of Administering Iodine to Patients Having Exophthalmic Goiter, J. A. M. A. **80**:1955 (June 30) 1923.

3. Porter, M. F.: Injection of Boiling Water in the Treatment of Hyperthyroidism, J. A. M. A. **61**:88 (July 12) 1913.

4. Crile, G. W.: The Thyroid Gland, Philadelphia, W. B. Saunders Company, 1922.

are ligation of the superior or inferior vessels, methods of injection, removal of small portions of the gland and the introduction of radium suggested by Terry.[5]

Many substances have been injected into enlarged thyroids for the purpose of destroying part of the gland. The literature concerning this procedure has been reviewed in a previous report.[1] The substances generally used for this purpose are: boiling water, as advocated by Porter;[6] urea and quinine sulphate, as proposed by Watson,[7] and a solution of phenol, iodine and glycerine, as used by Sheehan.[8] By far the most popular of these methods has been that of Porter, which, however, offers technical difficulties. Experiments by Barker[1] with many nontoxic solutions suitable for the purpose showed that absolute alcohol met all the requirements of a nonpoisonous coagulant to the thyroid, and it has been used on a series of patients with extremely toxic goiter, after all other methods had failed to cause sufficient improvement to allow a subtotal thyroidectomy without too great a risk.

In the experiments on animals, quantities of absolute alcohol of from 0.5 to 10 cc. were injected into the thyroid glands of dogs, and the glands were removed at intervals varying from fifteen minutes to two months. In these thyroids, coagulation necrosis was produced and, in turn, was replaced by fibrous scar tissue. The following technic was used for the injection of alcohol.

TECHNIC

The technic used for making injections into patients with goiter was that used in dogs, except that the injections were made under local anesthesia. A 2½ inch (6.27 cm.), 0.22 Luer needle and a 10 cc. Luer syringe were used for the injection of the alcohol, and a 1 inch (2.5 cm.), 18 bore needle was used for introducing the local anesthesia. A small wheal was raised in the skin by the injection of 1 per cent apothesine. This wheal was placed lateral to the median line of the body over the median line of the lobe in which the injection was to be made. The fingers of the left hand were next placed behind the sternomastoid muscle and the lobe, lifting the lobe anteriorly and medially. The small needle was introduced into the wheal, and a tract from there to the gland was infiltrated with the solution of apothesine. The large needle was then introduced along this tract into the gland. During the introduction of the needle and also during any subsequent movement of the needle in the gland, it was necessary that the needle be free from the syringe or any obturator so that bleeding would give evidence of the presence of large veins, and the alcohol would not be injected directly

5. Terry, A. I.: Radium Emanations in Treatment of Goiter, J. A. M. A. **76**:1821 (June 25) 1921.

6. Porter, M. F.: Boiling Water Injections into the Thyroid Gland for Hyperthyroidism, Surg. Gynec. Obst. **2**:1, 1915.

7. Watson, L. F.: Injection of Quinine and Urea Hydrochloride in Hyperthyroidism, J. A. M. A. **62**:126 (Jan. 10) 1914.

8. Sheehan, J. E.: Seventeen Cases of Goiter Treated with Injections of Carbolic Acid, Iodine and Glycerin, M. Rec. **92**:591 (Oct. 6) 1917.

into the circulation. The injection needle then entered the midportion of the lobe and was introduced well into its substance. It can easily be demonstrated that the needle is engaged in the gland by having the patient swallow, the skin acting as a fulcrum, while the long arm of the lever, the base of the needle, moves up and down (fig. 1 *C*). An obturator should be introduced into the needle before an injection is started to avoid blocking caused by the coagulation of blood and thyroid substance collected in the point of the lumen during its introduction. The desired amount of absolute alcohol was then introduced. The syringe was disconnected, the needle advanced about 2 cm. toward either pole and more alcohol was introduced, the process being continued until the lobe was satisfactorily infiltrated. The largest quantity of alcohol injected at one sitting was 30 cc.

RESULTS

In no case was an immediate or remote ill effect from the alcohol observed. On the day following the injection, and continuing until the third or fourth day, there was a rise in temperature and local evidence of aseptic reaction. The gland was increased in size, and this increase

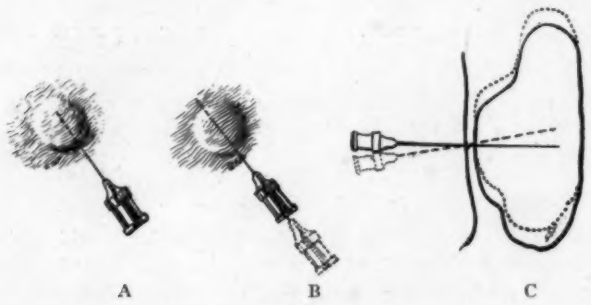

Fig. 1.—*A*, introduction of anesthetic, raising wheal; *B*, anesthetizing soft parts over gland; *C*, shows movement of needle during act of swallowing; this confirms the fact that the needle is in the gland.

subsided more slowly than the other evidences of local reaction. The enlargement was not sufficient to cause respiratory embarrassment from tracheal compression, nor was there any interference with the function of the recurrent laryngeal nerves.

Severe pain did not result from the injection in any case, although some patients complained of a sharp pain "like a toothache" back of the ear while the upper pole was being infiltrated. This lasted but a few moments. In one case pain was referred to the inferior mandibular division of the fifth cranial nerve on the side on which the injection was made. Most of the patients had several injections at varying intervals. The question of the amount of infiltration of the gland to be accomplished at a sitting must be decided by the condition of the patient. We have made injections into both lobes at one sitting in some patients

and into only one lobe or a portion of a lobe at one time in others. The process can be carried on indefinitely, if one wishes to do so, until the gland is reduced to a scar.

In the cases in which operation was performed, special care was taken in the microscopic study of the section to determine the effect of the injections. Since in some of them injections had been performed several times at long intervals, it was possible to contrast the changes from recent injections with those of earlier ones. The microscopic observations on these glands were similar to those made on the experimental animals. There was coagulation necrosis followed by a round

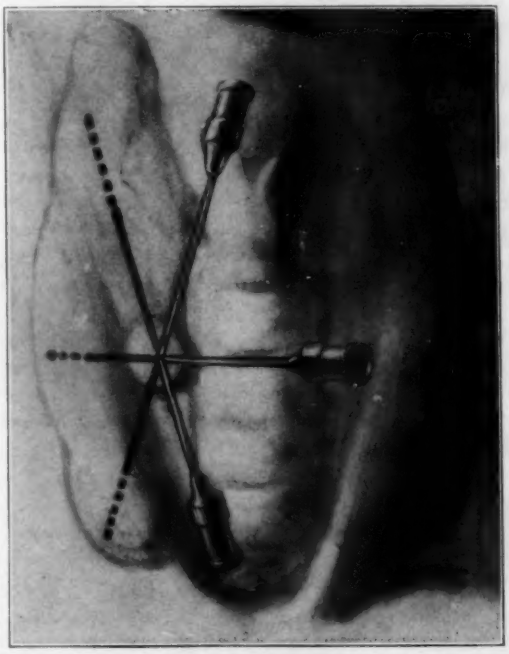

Fig. 2.—Position of needle during injection in different parts of the gland.

cell infiltration and fibroblastic proliferation and organization. Foreign body giant cells were found about bits of colloid which had been acted on by the alcohol, producing the reaction of a foreign body. The ultimate picture was one of fibrous tissue replacement of the destroyed thyroid tissue. The blood vessels passing through the injected area showed thrombosis, and in older areas organization of the thrombus with canalization. When numerous injections had been made, this factor alone must have meant considerable decrease in the blood supply of the gland.

The single objection to methods of injection is that the ultimate operative procedure is made more difficult by pericapsular adhesions.

These were more marked in the cases in which large amounts had been injected at one sitting, and were less marked in those in which there had been repeated injections of small quantities. This observation fits well with the experimental observation that the alcohol tends to leak out of the thyroid capsule around the injecting needle after the intracapsular pressure has been sufficiently raised. We believe that the technical difficulties of subtotal thyroidectomy will not be greatly increased by the injection of small quantities of alcohol on repeated occasions rather than a single large injection. We advise injections of from 8 to 16 cc. to a lobe repeated at weekly intervals, the number of injections being determined by the size of the gland.

ABSTRACT OF CASES

CASE 1.—*History.*—Mrs. B. M. L., aged 19, a clerk, entered the medical service of the hospital on Nov. 10, 1923, complaining of pain over the heart. The family history was unimportant, except that one brother had chorea. The patient had had frequent attacks of sore throat and one attack of rheumatic fever seven years before. Her ankles and knees were involved in this attack, and she was confined to bed for two weeks. She also had had scarlet fever four years before with uneventful recovery. A tonsillectomy had been performed three years previous to admission.

The present illness began with pain over the heart and palpitation fifteen months before she entered the hospital. Nine months before admission, an enlargement of the thyroid, which increased steadily in size, was noticed. This was associated with extreme nervousness and irritability. Jerky movements of the head and hands had been present for about six months before she came to the hospital. Her weight was 152 pounds (69 Kg.) in November, 1922, and at entrance to the hospital 117 pounds (53 Kg.). Beginning in June, 1923, she had received ten treatments with the roentgen ray, and had been given iodine for three months; during this time she was also placed on a low protein diet, and had much rest in bed.

Examination.—The patient was well developed, fairly nourished and rather restless, and irregular, jerky movements occurred in all parts of the body. Definite exophthalmos was present. The thyroid was enlarged, more on the right side, and it was of firm, uniform consistency. A definite bruit was heard over both lobes, but no thrill was felt. The heart was moderately enlarged. A faint systolic murmur was heard in the pulmonic area and a stronger one at the apex. The pulse rate was 130. The blood pressure was systolic 135 and diastolic 70. The extremities were normal, except for involuntary, irregular movements. The fingers showed a fine tremor.

Laboratory Examinations.—The urine was normal; the blood showed hemoglobin, 85 per cent; 4,490,000 erythrocytes, 6,200 leukocytes and a normal smear; the differential count showed a slight lymphocytosis. The basal metabolism rate was 58 per cent. The electrocardiogram showed an inversion of the T waves.

A diagnosis of exophthalmic goiter and chorea was made.

Treatment and Course.—The patient was treated in bed until May 24, 1924. During this time, she was given roentgen-ray irradiations over the thyroid. The basal metabolic rate varied from the rate at entrance to 70 per cent and fluctuated between this and 40 per cent. During April she had an acute infection of the

throat with acute arthritis of the knees and ankles, which aggravated all symptoms. The heart rate varied between 110 and 150 and was extremely labile.

On May 22, 1924, she was transferred to the department of surgery. She appeared nervous, and occasional choreiform movements were noted. The exophthalmos was now severe. Both lobes of the thyroid were large, and there was a loud bruit and thrill.

Roentgenograms of the chest showed some compression of the trachea by the goiter. The basal metabolic rate was 46 per cent; the average pulse rate was 130. The weight was 105 pounds (47.6 Kg.). The urine was normal. The blood showed hemoglobin, 56 per cent; 3,490,000 erythrocytes, and 6,900 leukocytes, with a slight relative lymphocytosis.

During her stay in the surgical ward the patient was in bed, on a 5,000 caloric diet, but she lost 3 pounds (1.4 Kg.) during the next week. On May 31, 16 cc. of absolute alcohol was injected into the right lobe of the thyroid; following this, there was considerable local reaction, including an increase in the size of the gland with redness and local heat. On June 1, the pulse rate was 160 and the temperature 101.4 F. Both the fever and the tachycardia gradually subsided, and on June 5, the temperature was normal and the pulse rate ranged between 100 and 110. On June 11, the weight was 105 pounds (47.6 Kg.). On June 19, the weight was 111 pounds (50.3 Kg.), and the patient was symptomatically much improved. On June 30, she weighed 121 pounds (55 Kg.), and the pulse was much more stable, about 110 in rate. The basal metabolism was 38 per cent. She was then allowed to be up and about the ward with a rest period of two hours a day in bed. She continued to improve symptomatically, and the pulse rate varied from 90 to 120 with exercise.

On July 25, impacted third molars were removed under nitrous oxide and oxygen anesthesia, while simultaneously 10 cc. of absolute alcohol was injected in each lobe of the thyroid. This was followed by a local and general reaction similar to, but less intense than, that at the previous injections. On August 4, she was discharged from the hospital weighing 130 pounds (59 Kg.). The basal metabolic rate was 27 per cent, and the average pulse rate, 100. She was advised to continue the high caloric diet and the rest period.

On November 10, the patient weighed 156 pounds (70.8 Kg.) and was greatly improved in every way. She was working as a clerk in a store. The pulse rate ranged from 90 in the morning to 120 in the evening after she had worked most of the day.

On December 7, the patient reported that she was feeling stronger, she weighed 159 pounds (72 Kg.), and the pulse rate ranged from 90 in the morning to 110 in the evening.

On January 28, 1925, the patient reported that she continued to work. The pulse readings on several consecutive days averaged 74 in the morning and 90 in the evening. The weight was 163 pounds (74 Kg.).

On July 1, 1925, she reported that she considered herself perfectly well.

CASE 2.—*History.*—Mrs. M. B., aged 52, a housewife, entered the hospital because of weakness, loss of weight and nervousness. She had had an operation for the removal of gallstones and the appendix. The menopause came four years before her admission to the hospital.

Examination.—The patient was fairly well nourished; the mental reaction was slow and she was nervous. The pupils were slightly irregular, and moderate exophthalmos was present. The thyroid was symmetrically enlarged, and was smooth and elastic. Thrills or bruits were not noted. The heart and lungs were essentially normal. The abdomen showed an old surgical scar over the superior

part of the right rectus abdominis. There was a marked fine tremor of the extended hands, but the extremities were otherwise normal. Her greatest weight had been 169 pounds (76.7 Kg.) six years before. Her weight on entrance was 102 pounds (46.3 Kg.). On February 8, the basal metabolic rate was plus 39.5 per cent and her average pulse rate was 112, after ten days' rest in bed.

Treatment and Course.—On this date a bilateral superior ligation of the thyroid was done, and a week later the patient was discharged for six weeks. She did not return until May 14, at which time she was somewhat improved, but she was still restless. The basal metabolic rate was plus 25 per cent; the average pulse rate, 100; her weight was 106 pounds (48 Kg.). On May 16, an alcohol injection was administered; 16 cc. was injected into the left lobe, and 6 cc. into the isthmus. There was little systematic reaction; her temperature reached 99.8 F. and the pulse rate was elevated to 120. This reaction subsided in two days, and the patient was discharged. She returned to the hospital on June 19, at which time she was less nervous. Her weight was 108 pounds (49 Kg.), and she had a basal metabolic rate of plus 23 per cent. Eight cubic centimeters of alcohol was injected into the right lobe, and the patient was discharged from the hospital on the following day. On July 22, she returned symptomatically improved: her weight was 110½ pounds (50 Kg.), her average pulse rate 100 and the basal metabolic rate plus 25 per cent. Eight cubic centimeters of alcohol was injected into each lobe; the patient was discharged the following day. She returned on October 2, and reported that she had been feeling well for the past two months, was gaining in weight and was almost completely relieved from nervousness. The basal metabolic rate was plus 15.1 per cent, and the average pulse rate, 76. Fourteen cubic centimeters of alcohol was then injected into the right lobe and 10 cc. into the left lobe. The patient was again discharged from the hospital on the day following the injection. She was considered cured and was advised that it would not be necessary for her to return to the hospital as long as she continued to gain in weight.

CASE 3.—*History.*—Mrs. E. B., aged 36, a housewife, entered the hospital on March 2, 1924, complaining of palpitation and loss of weight. The present illness began in November, 1923, with palpitation on slight exertion. Shortly after this she became nervous; this symptom increased up to the time of admission to the hospital. She believed that her eyes had become slightly more prominent during the two months before entrance to the hospital. Her best weight was 135 pounds (61.2 Kg.) in July, 1923; at entrance she weighed 105 pounds (47.6 Kg.). Vomiting and diarrhea had not occurred.

Examination.—She was extremely nervous, and had obviously lost some weight. Slight exophthalmos was noted. The thyroid was symmetrically enlarged, and a bruit could be heard over the entire gland. There was not any thrill. The lungs were normal, and the heart was not enlarged, but it was overactive. A blowing systolic murmur at the apex was transmitted to the base. Her blood pressure was: systolic, 130; diastolic, 72. The abdomen was normal. The extremities were normal except for a fine tremor of the fingers. The reflexes were normal. The blood Wassermann reaction was negative and the electrocardiogram was not definitely abnormal. Her blood showed a slight secondary anemia.

Treatment and Course.—She was placed in bed and given a high caloric diet and sedatives. On March 16, her weight was 106 pounds (48 Kg.), the basal metabolic rate, 52 per cent and her average pulse rate, 100. On this date, 10 cc. of absolute alcohol was injected into each lobe. This was followed by a moderately

severe reaction, and on March 19 she went home. On May 14, she returned to the hospital. Her weight was 118 pounds (53.5 Kg.), her basal metabolic rate was 38 per cent and the pulse rate averaged 90. The symptoms were much less severe. On May 15, 10 cc. of absolute alcohol was injected into each lobe of the thyroid. She left the hospital on the following day. On July 1, her weight was 124 pounds (56 Kg.), her basal metabolic rate was 26 per cent and she was much improved. Ten cubic centimeters of absolute alcohol was injected in each lobe, and she again returned home. On August 2, her weight was 136 pounds (61.7 Kg.), her basal metabolic rate was 10 per cent and she was entirely free from nervousness, but still had some palpitation on exertion. On September 15, she weighed 140 pounds (63.5 Kg.), and considered herself entirely well. She

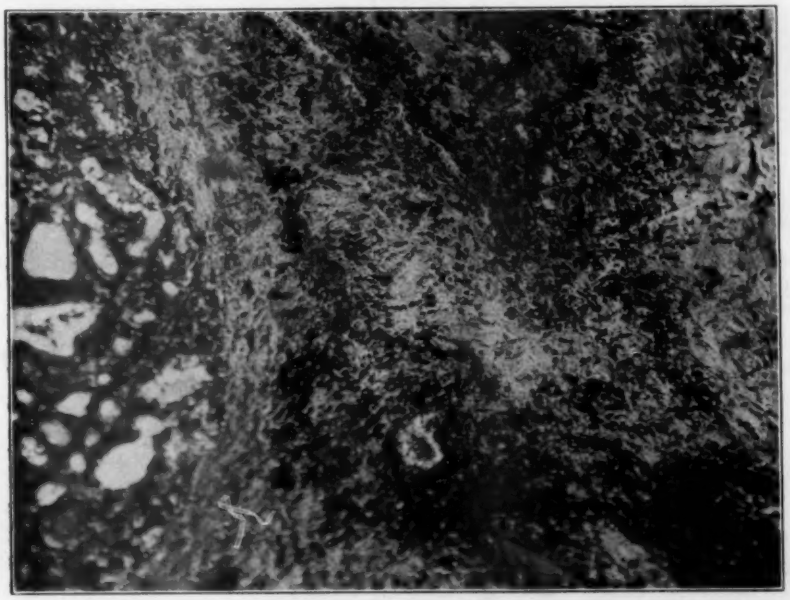

Fig. 3 (case 4).—Border of almost completely healed area of necrosis following alcoholic injections.

reported by letter in February, 1925, that she was still in what she considered a normal condition.

CASE 4.—*History.*—Mrs. O. W., aged 33, a housewife, entered the hospital on Nov. 20, 1923, complaining of enlargement of the neck, nervousness and loss of weight. The patient gave a history of having had some fulness in the neck for eleven years. Her general health was good until three years before, when the neck suddenly began to increase in size and she noticed marked weakness, an increase in appetite and burning and smarting of the eyes. The symptoms had gradually increased, with added prominence of the eyes, extreme nervousness and loss of weight.

Examination.—The patient was undernourished. Her skin was warm, moist and somewhat pale. Marked exophthalmos was present. Both thyroid lobes were markedly enlarged; some hard nodules were felt in the gland. Thrill and bruit over the gland and pulsation of the large vessels of the neck were marked. The

heart was somewhat enlarged and overactive. The sounds were normal and regular; the pulse rate was 120. Her blood pressure was: systolic, 120; diastolic, 60.

The extremities and reflexes were normal. There was a marked fine tremor of hands on extension. Her weight was 97 pounds (44 Kg.). The basal metabolic rate was plus 75.5 per cent.

The diagnosis was exophthalmic goiter.

Treatment and Course.—The patient was placed in bed on a high caloric diet for three weeks, but she did not improve. On December 13, both superior thyroid vessels were ligated under gas and oxygen anesthesia. There was a moderately severe reaction which subsided in three days. She continued in bed under observation until Jan. 3, 1924, when she was discharged for six weeks. At the time of discharge the basal metabolic rate was plus 75 per cent, weight, 98½ pounds (44.7 Kg.), and average pulse rate, 110.

On March 18, the patient returned to the hospital with an average pulse rate of 110; weight, 98 pounds (44.5 Kg.), and basal metabolic rate, plus 55 per cent. Her condition was somewhat improved, but she continued to be extremely nervous. The case was not considered a good operative risk. On March 20, 8 cc. of absolute alcohol was injected into the left thyroid lobe. A moderate general reaction followed this procedure, the temperature reached 101.5 F., and pulse rate, 120. This subsided in three days.

On March 29, 10 cc. of alcohol injected into the right lobe resulted in little general reaction; the patient was discharged three days later.

On May 28, the patient returned to the hospital symptomatically much improved. The weight was 112 pounds (50.8 Kg.), the pulse rate, 90 and the basal metabolic rate, plus 26.2 per cent. The case would have been a good operative risk at this time, but we wished to learn whether further improvement could be made, and whether it would be permanent. On May 31, 14 cc. of absolute alcohol was injected into the right lobe and isthmus. A reaction did not occur, and the patient was discharged on June 2.

On July 24, the patient returned, stating that she had been working hard since leaving the hospital early in June. She had lost 13 pounds (6 Kg.), and the pulse rate averaged 110. She was more nervous, and the basal metabolic rate was plus 65 per cent. Her weight at this time was 109 pounds (49.4 Kg.). On July 28, 10 cc. of alcohol was injected into each thyroid lobe; the patient was allowed to return home on July 30.

On November 14, the patient returned to the hospital. She had been carrying on her ordinary work without marked symptoms or further loss of weight. Her pulse rate averaged 100, the basal metabolic rate, plus 40 per cent and her weight, 108½ pounds (49.2 Kg.). The operative risk was considered good at the time, and we felt that the patient would not be able to carry on satisfactorily without a partial thyroidectomy.

On November 24, a subtotal thyroidectomy was performed. Convalescence was uneventful. The pathologic report was: "Nodular goiter with scattered areas of exophthalmic hypertrophy. Colloid on whole fairly abundant."

In July, 1926, the patient returned to the hospital for examination. There was no evidence of hyperthyroidism. The basal metabolic rate was 6 per cent and her weight was 130 pounds (59 Kg.).

CASE 5.—*History.*—J. D., aged 49, a mechanic, was admitted to the medical department of the hospital on Feb. 29, 1924, complaining of weakness, loss of weight and palpitation. In December, 1923, he began to lose weight and became weak and nervous. In January, 1924, he developed a severe diarrhea which lasted

two weeks. His eyes became prominent. The symptoms increased in severity until the time of his entrance to the hospital. His weight in December, 1923, was 145 pounds (65.8 Kg.), and at admission, 116 pounds (52.6 Kg.).

Examination.—The patient was undernourished and extremely nervous and his skin was moist. The eyes were normal, except for a moderate degree of exophthalmos. There was a bilateral enlargement of the thyroid, more marked on the right; the gland was uniform in consistency, and a definite bruit was heard over both lobes. Both lungs were normal. The heart was slightly enlarged; a blowing systolic murmur was heard loudest in the fourth intercostal space and was transmitted to the base of the heart. The blood pressure was: systolic, 128; diastolic, 60. The abdomen was normal, except for tenderness over the right upper quadrant. The genitalia, rectum and reflexes were normal. The fingers

Fig. 4 (case 5).—Low power photomicrograph of large area of necrosis in thyroid; localized epithelial hypertrophy and hyperplasia of lymphoid tissue.

showed a fine tremor. The basal metabolic rate was 61 per cent, and the pulse rate averaged 108. The electrocardiogram showed ventricular extrasystoles. The urine was normal. An orthocardiogram showed an index of 141 per cent with widening of the aortic arch.

Treatment and Course.—Treatment consisted of rest, sedatives and a high caloric diet. On March 15, his basal metabolic rate was 40.5 per cent. At this time, auricular fibrillation was noted, which was present intermittently during his stay in the hospital. On April 7, his basal metabolic rate was 50 per cent, and on April 26, it was 42 per cent. During March and April, three roentgen-ray treatments were given.

On May 9, he was transferred to the department of surgery. At this time, examinations showed that his condition was about the same as it was at entrance to the hospital, and the patient did not show symptomatic improvement. Auricular fibrillation was still present, and his weight was 112 pounds (50.8 Kg.).

On May 12, the basal metabolic rate was 51 per cent. On May 13, 6 cc. of absolute alcohol was injected into each lobe. No appreciable reaction occurred, and he was sent home on May 15.

On June 16, he returned to the hospital unimproved. The basal metabolic rate was 55.2 per cent, the average pulse rate, 112, and the weight, 116 pounds (52.6 Kg.).

On June 18, 10 cc. of absolute alcohol was injected into each lobe without any reaction; the patient was sent home on June 22.

On September 3, 1924, he returned showing symptomatic improvement. His weight was 124 pounds (56.2 Kg.), but the basal metabolic rate which was 53 per cent, and his average pulse rate of 110 did not show improvement. On September 15, a subtotal thyroidectomy was done. The convalescence was uneventful, except for auricular fibrillation during the first three postoperative days. The

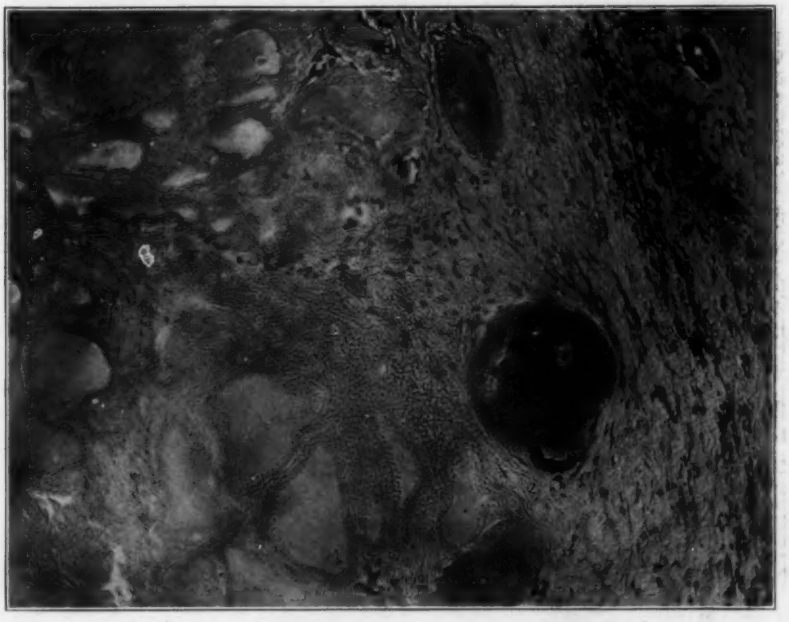

Fig. 5.—High power detail of border of area of necrosis seen in figure 4; simple necrosis of thyroid acini, surrounded by reactive zone of healing; early encapsulation.

pathologist reported: "Tissue weighs 49 grams. There is a marked hyperplasia of the rudimentary lymphoid tissue and areas of epithelial hypertrophy. The picture is that of exophthalmic goiter. There are areas of complete necrosis of the thyroid tissue surrounded by a definite capsule."

He was seen in August, 1926, at which time he was in excellent condition. His weight was 147 pounds (66.7 Kg.), his basal metabolic rate was 10 per cent and his pulse rate was 80. Exophthalmos had disappeared, and he was free from symptoms.

CASE 6.—*History.*—Mrs. E. M., a housewife, aged 44, came to the hospital Aug. 29, 1923, complaining of enlargement of the neck, nervousness and loss of weight. In March, 1923, she first noticed the nervousness. Since the onset of these first symptoms, she had lost 25 pounds (11.3 Kg.), and had noticed an

increasing prominence of the eyes. During the six weeks before admission, shortness of breath had been noted.

Examination.—The patient was poorly nourished, nervous and irritable. The skin was moist. Marked exophthalmos was present. There was bilateral symmetrical enlargement of the thyroid. A definite bruit could be heard over the gland.

The lungs were normal. The heart was slightly enlarged; the pulse rate was 148, and it was regular. A systolic murmur was heard over the apex and in the mitral area. The blood pressure was systolic 120 and diastolic 60.

The abdomen was normal. There was a fine tremor of the extended hands. Reflexes were present, and were prompt and equal on the two sides. Her weight on admission was 100 pounds (45.4 Kg.).

Treatment and Course.—On admission to the medical ward, the treatment consisted of rest, a high caloric diet and sedatives.

On September 2, the basal metabolic rate was 78 per cent, and the average pulse rate was 122. On September 18, the basal metabolic rate was 58.5 per cent and the average pulse rate was 116; on September 27, the basal metabolic rate was plus 56 per cent and the average pulse rate was 102.

On October 4, both superior thyroid vessels were ligated, and on October 14, the patient was discharged for six weeks. When she left the hospital, her weight was 92 pounds (41.7 Kg.).

The patient returned to the hospital November 2. She weighed 93¼ pounds (42.5 Kg.), the average pulse rate was 92, and the basal metabolic rate was plus 36 per cent. It was thought that the patient would make further gain; so she was discharged.

On February 24, 1924, she returned to the hospital with a basal metabolic rate of plus 48 per cent, and an average pulse rate of 112. She weighed 98 pounds (44.5 Kg.), and symptomatically had somewhat improved since ligation. During this visit to the hospital, septic tonsils were removed.

On July 18, the patient returned with an average pulse rate of 132, a basal metabolic rate of 61.6 per cent, and a weight of 106 pounds (48.1 Kg.). The nervousness was more marked than on the previous visit. On July 22, 12 cc. of absolute alcohol was injected into the right lobe and 8 cc. into the left. A reaction did not occur and the patient was discharged the following day.

A second alcoholic injection was given on August 15, 8 cc. into each lobe. At the time of this injection the basal metabolic rate was plus 51 per cent, the average pulse rate was 115 and the weight was 110 pounds (50 Kg.).

On November 18, the patient again returned to the hospital. In spite of the fact that she had been working hard, the basal metabolic rate was lower than on any previous occasion—plus 32 per cent; the average pulse rate was 100 and the weight was 115 pounds (52 Kg.). The patient was considered in good condition for operation, and on November 28, subtotal thyroidectomy was done. Convalescence was uneventful. The pathologist reported: "Adenomatous colloid goiter with hyperplasia of the rudimentary lymphnodes.

CASE 7.—*History.*—Mrs. A. D., aged 38, a housewife, was admitted to the medical service of the hospital on Aug. 31, 1924, complaining of loss of weight and prominence of the eyes.

In January, 1924, palpitation and nervousness were first noticed. In April, her eyes began to be prominent, and they continued to become more so until her admission. Her weight had decreased from 138 to 106 pounds (62.6 to 48 Kg.). She perspired freely. In April, the right superior thyroid vessels had been ligated at another hospital without benefit.

Examination.—She was fairly well nourished, but showed evidence of loss of weight. The skin was brownish, warm and moist. There was a high grade of exophthalmos. The thyroid gland was symmetrically enlarged and of uniform consistency. A thrill was felt at the superior poles, and a loud bruit was present. The lungs were normal. The heart was enlarged to the left, and a blowing murmur, systolic in time, was heard loudest at the apex and faintly in the aortic and pulmonary areas. The average pulse rate was 126, and it was regular. The abdomen was normal. The extremities showed a marked tremor of the fingers and edema of both ankles. The reflexes were normal. The laboratory examinations showed normal urine. The Wassermann reaction was negative. The sugar tolerance test showed a slightly increased fasting sugar and a slight lag in the sugar curve. The basal metabolic rate was 67 per cent. The electrocardiogram showed sinus tachycardia with flat T waves.

Fig. 6 (case 7).—Low power photomicrograph of area of hemorrhagic necrosis with border of organization.

Treatment and Course.—The patient remained in bed on a high caloric diet until October 3. During the early part of this period the patient's symptoms became somewhat less marked, and the basal metabolic rate on September 10 was 51 per cent, and the average pulse rate, 108. After this the symptoms increased in intensity, and on September 26, the basal metabolic rate was 70 per cent, and the pulse rate averaged 126. She was transferred to the surgical service on October 3, when 20 cc. of absolute alcohol was injected into each lobe of the thyroid. That evening her temperature was 102.8 F., and the pulse rate was 140. On October 5, the temperature was normal. She was discharged on October 9. Her weight then was 103 pounds (46.7 Kg.).

On October 31, she reported by letter that her weight was 116 pounds (52.6 Kg.), that the pulse rate averaged 130 and that some edema was present on the ankles.

On November 22, another report stated that there was definite improvement in symptoms. Her weight was 123 pounds (56 Kg.), and the average pulse rate was 120.

On Jan. 20, 1925, she returned to the hospital. She weighed 138 pounds (62.6 Kg.); the pulse rate was from 110 to 120, and there was a definite improvement in symptoms. The basal metabolic rate was 36 per cent. The case was considered a good operative risk, and on January 31, a subtotal thyroidectomy was done. A moderately severe reaction was followed by a normal convalescence. The pathologist reported: "Epithelial hypertrophy with marked lymphoid hyperplasia. Larger area of recent necrosis or infarction." Reports received in July, 1926, indicated the patient was well at that time and weighed 160 pounds (72.6 Kg.).

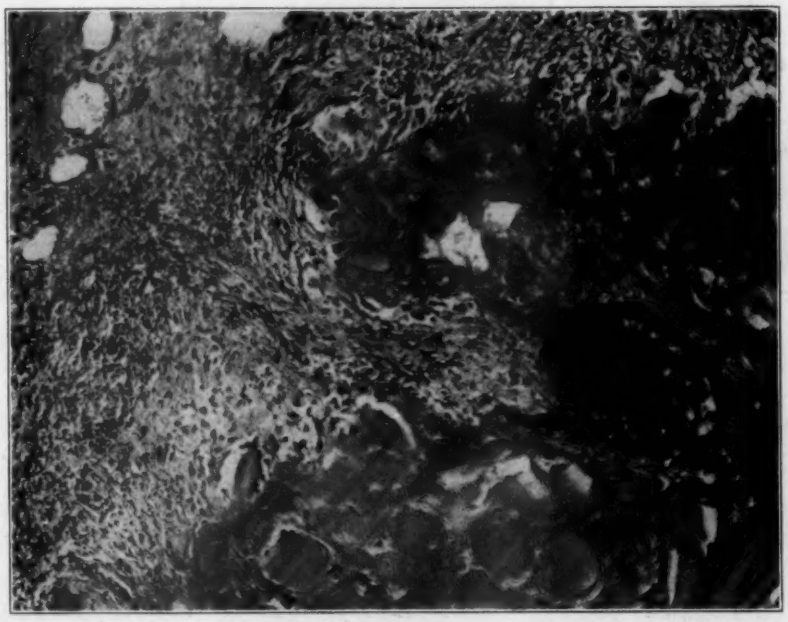

Fig. 7 (case 7).—High power detail of border of organization of necrotic area of thyroid.

CASE 8.—*History.*—H. W., aged 50 a farmer, came to the hospital Feb. 21, 1924, complaining of enlargement of the neck, nervousness and muscular weakness. His present illness began in July, 1922, with weakness. This became progressively worse until May, 1923, when enlargement of the neck was noticed. In July, he became nervous and noticed palpitation, and his eyes became prominent. In October, he became short of breath. His best weight was 160 pounds (72.6 Kg.) in July, 1922, and his weight at the time of entering the hospital was 106 pounds (48 Kg.). His appetite was good, and there had not been any vomiting or diarrhea.

Examination.—He was nervous and undernourished, and presented a severe degree of exophthalmos. The tonsils were hypertrophied. The thyroid was slightly enlarged, more noticeably on the right; there was no thrill, but a loud bruit could be heard over the entire gland. The lungs were normal. The heart

was moderately enlarged, with a heaving of the precordium; a blowing systolic murmur was heard at the apex and was transmitted to the base; the pulse rate was 120, and it was regular. The blood pressure was 140 systolic and 60 diastolic. The peripheral vessels were sclerotic.

The abdomen was normal. There was tremor of the extended fingers; the reflexes were active. Laboratory examination showed that the urine was normal. The electrocardiogram showed sinus tachycardia. The basal metabolic rate was 70 per cent. The patient was admitted to the medical service with a diagnosis of exophthalmic goiter and chronic myocarditis.

Treatment and Course.—The patient was considered a poor operative risk, and treatment consisted of rest in bed and a high caloric diet. He did not improve during ten weeks of this treatment. On May 16, the basal metabolic rate was 67 per cent, and the average pulse rate, 110. On this date 10 cc. of absolute

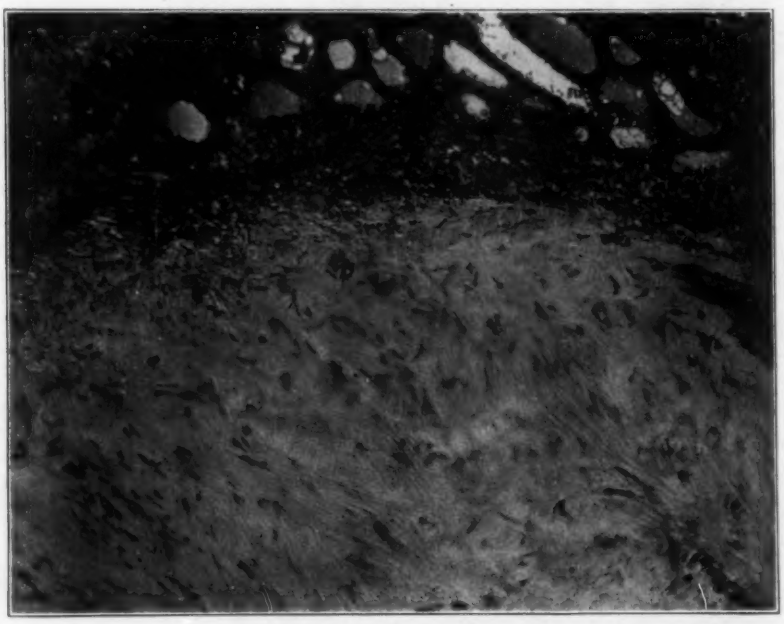

Fig. 8 (case 7).—Border of dense scar tissue around another large area of necrosis connected with necrotic adenoma; advanced encapsulation.

alcohol was injected into each lobe of the thyroid. A moderately severe general reaction followed, but subsided after three days. The patient was discharged; he weighed 104 pounds (47.2 Kg.).

On September 16, he returned to the hospital weighing 125 pounds (56.7 Kg.) and showing much symptomatic improvement. The basal metabolic rate was 50 per cent, and the average pulse rate was 94. On this date, 14 cc. of absolute alcohol was injected into each lobe of the thyroid. There was a slight reaction, and he was discharged from the hospital on September 17.

On October 20, he returned. He weighed 127 pounds (57.6 Kg.), and was much less nervous. The basal metabolic rate was 47 per cent and his average pulse rate was 90. On October 22, 12 cc. of absolute alcohol was injected into each lobe, and was followed by little reaction. He left for home the following day.

He returned on December 11 when his general condition was about the same. The basal metabolic rate was 50 per cent; his weight was 143 pounds (65 Kg.), and the pulse rate averaged 90. On Jan. 15, 1925, he was in about the same general condition, but the operative risk was thought to be good, and a subtotal thyroidectomy was done. Convalescence was uneventful. The specimen removed showed: "epithelial hypertrophy, hyperplastic rudimentary lymph nodes with large areas of necrosis."

In July, 1926, he reported that he was in excellent condition.

CASE 9.—*History.*—Miss J. Mc., aged 34, a stenographer, came to the hospital on May 28, 1924, complaining of weakness and nervousness. A sister had had exophthalmic goiter. The present illness began in February, 1924, with nervousness and enlargement of the neck. In April, she began to have palpitation and dyspnea on exertion. Her best weight was 124 pounds (56.2 Kg.) in October, 1923, and she weighed 105 pounds (47.6 Kg.) at the time of entrance. Her appetite was voracious, and diarrhea and vomiting had not occurred.

Examination.—She was undernourished and nervous. There was a moderate grade of exophthalmos. The thyroid gland was symmetrically enlarged, without a thrill or bruit. The lungs were normal; the heart was slightly enlarged and overactive. The blood pressure was: systolic, 130; diastolic, 68. The abdomen was normal. The extremities were normal, except for a tremor of the fingers. Laboratory examination showed normal urine, a negative blood Wassermann reaction and slight secondary anemia. An electrocardiogram showed sinus tachycardia. The basal metabolic rate was 62 per cent.

Treatment and Course.—She was placed in bed on a high caloric diet. She improved somewhat, and on June 10, the basal metabolic rate was 43 per cent, and the pulse rate, 100. On June 25, the basal metabolic rate was 49 per cent. She had continued to lose weight, until at this time she weighed 99 pounds (45 Kg.). On June 26, 10 cc. of absolute alcohol was injected into each lobe of the thyroid. There was a moderate reaction, and she was discharged on July 1.

On July 17, the patient reported by letter that she was improving. On August 30, she wrote that she felt well and had been working several hours a day, against our advice.

On September 10, she returned; her weight was 104 pounds (47.2 Kg.), and the basal metabolic rate, 35 per cent. Ten cubic centimeters of absolute alcohol was injected into each lobe. There was little reaction, and she was discharged two days later.

On October 15, her weight was 108 pounds (49 Kg.), the basal metabolic rate was 38 per cent and the average pulse rate was 100. Fifteen cubic centimeters of absolute alcohol was injected into the right lobe and 10 cc. into the left lobe. She returned home the following day.

On November 19, her weight was 112 pounds (50.8 Kg.), the basal metabolic rate, 25 per cent, and the average pulse rate, 90. Symptomatically, she was much improved. On December 20, her weight was 120 pounds (54.4 Kg.), the basal metabolic rate, 27 per cent, and the average pulse rate, 90.

At this time, a subtotal thyroidectomy was done without bad results, and her convalescence was without event. The specimen showed: "epithelial hyperplasia and hypertrophy. Hyperplasia of the rudimentary lymph nodes. Large areas of necrosis with beginning organization."

In January, 1927, the patient reported that she was in good condition.

CASE 10.—*History.*—Mrs. L. R., aged 52, a housewife, entered the hospital Jan. 23, 1924, complaining of weakness, loss of weight and exophthalmos.

Twenty years before she had had an illness accompanied by a rapid pulse, loss of weight and marked nervousness. During this attack, her eyes had become prominent. After spending seven months in bed, she had improved, and while she had not been entirely well she had carried on her usual duties. In November, 1923, she had again become nervous, and the exophthalmos had become more marked. Her weight was reduced from 128 to 108 pounds (58 to 49 Kg.).

Examination.—She was nervous and emaciated. Extreme exophthalmos was noted. The thyroid was slightly enlarged and very firm. Definite thrill and bruit were observed. The lungs were normal. The heart was moderately enlarged and overactive, and the pulse rate was 130. A blowing systolic murmur was loudest over the mitral area. The blood pressure was 138 systolic, and 68 diastolic. The abdomen was normal. The extremities were normal except for tremor of the fingers.

Laboratory Observations: The urine was normal. An electrocardiogram showed sinus tachycardia. The basal metabolic rate was 76 per cent.

The diagnosis was acute exacerbation of a chronic type of exophthalmic goiter.

Illness and Course.—She was placed in bed, and given sedatives and a high caloric diet.

On February 10, she had not improved, and the superior thyroid vessels on both sides were ligated. This was followed by a moderately severe reaction. A few days later, she was sent home.

She returned on April 10, without symptomatic improvement. Her weight was 100 pounds (45.4 Kg.), and the basal metabolic rate was 70 per cent. On April 12, 10 cc. of absolute alcohol was injected into each lobe. There was a mild reaction, and she was discharged a week later.

On June 2, she returned, somewhat improved. Her weight was 105 pounds (47.6 Kg.), and the basal metabolic rate was 54 per cent. Ten cubic centimeters of absolute alcohol was again introduced into each lobe, and she was sent home.

On July 12, she returned, showing further improvement. Her weight was 110 pounds (50 Kg.), and the basal metabolic rate was 45 per cent.

She was not seen again until 1925, when she stated that she had felt fairly well from August, 1924, until January, 1925, and had carried on her usual work. Since January, she had had a return of symptoms; she weighed 105 pounds (47.6 Kg.), and the basal metabolic rate was 65 per cent. The right lobe was removed, and a sharp reaction followed. She went home with instructions to return, but she did not do so until Feb. 23, 1926. There had been so much relief from the lobectomy that she had considered herself well until December, 1926, when the symptoms returned. The basal metabolic rate was 75 per cent, and the weight 103 pounds (46.7 Kg.). The left lobe was removed; this was followed by a severe reaction. She was seen in January, 1927, and was in good condition. The basal metabolic rate was 12 per cent, and she weighed 120 pounds (54.4 Kg.).

COMMENT

Ten patients were treated by the foregoing method. Some of them had been under observation for as long as two years. In most cases the operative risk was considered poor at the onset of treatment. All except the patient in case 10 showed marked symptomatic improvement, with gain in weight, decrease of nervousness and decrease of pulse rate. Some diminution of the basal metabolic rate was noted, but this was not

remarkable in many of the cases. In seven cases the eventual improvement was sufficient to class the patients as good operative risks, and subtotal thyroidectomies were performed. Three patients improved so much after several injections that further treatment was not necessary. All of these patients rested in bed for long periods, under supervision, without marked improvement, while in some instances the symptoms actually increased in severity. The patients were selected from the group of patients who did not show sufficient improvement under recognized methods of treatment to allow lobectomy or subtotal thyroidectomy. Some of them had received roentgen-ray therapy; others had been treated by superior pole ligation, but in every case enough time had elapsed after these measures had been employed to determine the maximum improvement before the injection of alcohol was begun. With the present method of treating patients with severe hyperthyroidism, this procedure is not commonly needed, but we believe that it can be used advantageously in a small group of patients who do not respond to the usual preoperative treatment. Since the completion of these studies, approximately 1,600 patients with goiter have been treated surgically in this clinic. Of this group, fourteen patients were treated also with alcohol as a preoperative measure, with results similar to those here reported.

SUMMARY AND CONCLUSIONS

1. Absolute alcohol can be injected into the thyroid of patients with hyperthyroidism without harm to them.

2. The local histologic changes are similar to those found in the experimental animals: an initial coagulation necrosis, followed eventually by replacement of the thyroid tissue by fibrous tissue.

3. The procedure is without technical difficulties.

4. The local and general reactions are slight.

5. An improvement in the patient's condition can be produced, depending on the amount of gland destroyed by the alcohol.

6. The procedure is not intended to replace subtotal thyroidectomy, but is applicable in a small group of cases in which all other methods have failed to make the operative risk good.

7. Periglandular adhesions result, which make the complete operation more difficult, but by the use of small amounts of the alcohol injected frequently this can be made a negligible factor.

THE INTERNAL CALLUS

AN EXPERIMENTAL STUDY *

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The term "internal callus" is employed frequently by those who treat patients who have sustained fractures; this and other names are mentioned in textbooks. Blaisdell and Cowan described it in a series of experiments on kittens.[1] The late Dr. Edward Hall Nichols conducted a series of experiments on animals to demonstrate the internal callus, which he showed to me shortly before his death, but I believe they have never been published. The experiments I have conducted were prompted by those of Dr. Nichols.

Fig. 1 (cat 42).—Cross-section of the tibia at the site of operation, showing the hole in the cortex plugged with bone and fibrous tissue.

In the roentgenograms showing healing fractures one sees little, if any, internal callus. It was absent in several series of experimental fractures of the humeri of cats, or was occasionally present in a rudimentary degree.[2] In these fractures, of course, much deformity and overriding were unavoidably present, and all nature's effective efforts at healing were expended on the outside of the cortex beneath the periosteum. The internal callus is supposed to be more in evidence in frac-

* From the Stanford University Laboratory of Surgical Research.

1. Blaisdell, T. E., and Cowan, J. F.: Healing of Simple Fracture, Arch. Surg. **12**:619 (March) 1926.

2. Ely, Leonard W.: An Experimental Study of the Healing of Fractures, Arch. Surg. **5**:527 (Nov.) 1922.

tures with accurate apposition; this is possibly true, but is difficult to demonstrate, if the fracture is a complete one.

The problem that interested me was the method of repair of an injury to the shaft of a long bone when there was no actual solution of continuity, and therefore no necessity for nature to build a wiped joint, so-called, under the periosteum—the method she employs when the shaft is completely fractured. I selected cats for the experiment, cut down on the anteromedial aspect of the shaft of the right tibia, incised the peri-

Fig. 2 (cat 36).—Note the bridge of fibrous tissue at the surface, the incomplete bridge of bone trabeculae farther in, the new bone trabeculae along the cut surfaces of the cortex and the scattered trabeculae in the marrow canal.

osteum, and with a small drill bored a hole about 2.7 mm. in diameter into the marrow canal. Then I closed the wound and applied a collodion dressing. All operations were performed under complete ether narcosis and with strict asepsis. The cats died or were killed at various intervals. The bone was removed, fixed in 10 per cent formaldehyde, decalcified in 5 per cent nitric acid, run through the alcohols and ether, and mounted

in celloidin. I operated on eleven cats, but in six of them the wounded area could not be identified. The results in the other five are given in detail. There were no infections of the bone.

PROTOCOLS

CAT 36.—This cat was examined sixty-seven days after operation. The hole in the cortex was plugged with fibrous tissue, which was continuous with the periosteum, and streamed down in a long band through the marrow canal almost

Fig. 3 (cat 40).—The illustration shows the new trabeculae at the side of the hole, on the outside of the cortex, and the incomplete bridge of new trabeculae across the hole near the surface, with fibrous tissue and scattered bone trabeculae deeper in. A second incomplete bridge of new bone trabeculae has formed in the marrow canal below the level of the cortex.

to the opposite cortex. In it, as it passed through the hole in the cortex, several larger and smaller areas of bone had formed. Bone trabeculae had also formed at the sides of the hole on the cut ends of the cortex, and this new layer of bone was continuous with one of considerable thickness on the outside of the cortex under the periosteum, and also with another much thinner, on the inside of the cortex. There was no suggestion of bridging of bone across the gap at the surface.

CAT 40.—This cat was examined thirteen days after operation. Near the surface, between the cut margins of the cortex there was an irregular mass of fibrous tissue across the gap, continuous with the periosteum, and this fibrous tissue extended irregularly down into the hole. In its superficial portion, almost at the outside level of the cortex, a bridge of new trabeculae was forming Deeper in the hole numerous trabeculae were building up, apparently from the fibrous tissue; just below the level of the inner cortex these trabeculae were much thicker and had formed an almost complete bridge across the gap. At a short distance below them, well out in the marrow cavity, another new island of bone

Fig. 4 (cat 41).—New bone trabeculae on the outside of the cortex. The hole is plugged with fibrous tissue with scattered bone trabeculae. Many new trabeculae have formed beneath the level of the cortex, but the ones in this particular slide do not show much bridging across.

was developing in fibrous tissue. Scarcely any bone was developing on either of the cut surfaces seen in the slide. At one side of the gap new trabeculae were developing on the outside of the cortex, but these did not appear on the other side.

CAT 41.—This cat was examined fourteen days after operation. The soft parts of the bone had been removed over the hole in the preparation of the specimen, so that the question of the continuity of the periosteum could not be determined. A marked poliferation of bone had taken place on the outside of the cortex for

some distance on each side of the hole; as usual it was thicker in the immediate vicinity of the hole, and tapered off as the distance from the hole increased. Many trabeculae were seen in the fibrous marrow beneath the level of the cortex, and these formed an incomplete bridge across the hole below the level of the cortex, in the fibrous marrow. Evidence of any new formation of bone on the cut margins of the cortex could not be seen. The inner aspect of the cortex near the hole also showed some new bone trabeculae.

CAT 42.—This cat was examined thirty-four days after operation. When the skin was removed from the leg of the animal after death, a distinct soft mass

Fig. 5 (cat 42).—The hole has been bridged across at the surface by fibrous tissue, and in the deeper portion of this fibrous tissue an incomplete bridge of new bone trabeculae has formed, continuous with the new bone layer formed on the cut margins of the cortex. Scattered trabeculae can be seen deeper in the cut and many also below the opening, in the marrow canal.

appeared under the deep fascia at the site of the wound. This had the appearance of the ordinary cheesy material occasionally found after operations on animals whose wounds are infected, but there was no other sign of infection.

The periosteum passed across the hole and continued through its center as a rather thin strip of fibrous tissue which extended into the marrow canal. Bone trabeculae were forming in the bone in this fibrous strip. A thin strip of bone had been laid down on each side of the cut surfaces of the bone, and this was

continuous with the new trabeculae formed in the hole. Trabeculae were especially noticeable just beneath the periosteum, but many had formed beneath in the marrow canal. Distinct evidence of external callus could not be seen.

CAT 43.—This cat was examined forty-two days after operation. The periosteum stretched across the hole, and directly beneath this, in the fibrous tissue, an almost complete bridge of bone trabeculae had developed. New bone had also formed on the cut surface on each cortical margin. A few trabeculae were scattered in the cellular marrow which occupied the rest of the hole. The blood sinuses were distended with blood cells. A few other trabeculae were present

Fig. 6 (cat 43).—Note the strip of fibrous tissue across the hole at the surface with the almost complete bridge of bone beneath it. Deeper, scattered trabeculae can be seen.

in the marrow beneath the hole, but these were not as numerous as in some of the other specimens. No new formation of bone was present on the outside of the cortex.

SUMMARY

When a hole is bored into the cortex of a long bone of an animal it becomes filled with fibrous tissue which is continuous with the periosteum and often extends well down into the marrow canal. Instead of forming a barrier to bony union, this formation of fibrous tissue is evidently a

step in the healing process. In it bone trabeculæ form irregularly. Sometimes they are most numerous near the surface of the cortex, sometimes in the hole and occasionally in the marrow beneath the hole. Often new bone is formed on the outside of the cortex, but this seems to play little, if any, rôle in the filling up of the hole. It may be absent. I have not observed any necrosis of the cut margins of the cortex as described in many textbooks. Contrary to what I had believed before, bone is actually produced on the cut margin of the cortex. Cartilage was absent in the healing process.

CEREBROSPINAL FLUID

NORMAL VARIATIONS IN THE RATE OF FORMATION *

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During the routine care of neurosurgical patients with obstructive hydrocephalus, periodic drainage of the ventricles has been necessary for the relief from intracranial pressure in a number of cases. It has been noted repeatedly that in the early morning the symptoms of pressure develop much more slowly, and, furthermore, that after longer periods of time, drainage of the ventricles yields less fluid than at other times during the day. This has been observed so constantly that at present it is customary to allow these patients to go from midnight until 8 or 9 a. m. without drainage. Even then the intracranial pressure and the quantity of fluid obtained is less than after a four to six hour interval during the later part of the morning or evening.

The most striking illustration of this diurnal and nocturnal variation in the formation of ventricular fluid was given by a patient in whom continuous drainage of the cisterna magna and ventricles was established because of obstruction about the base of the brain (case 1). Figure 1 shows an almost total absence of drainage in the hours immediately after midnight, while there is a noticeable decrease in the amount of fluid in the early afternoon. On the other hand, the largest amount of fluid was obtained in the morning and evening hours from 7 or 8 to 12 o'clock.

In the only other case of continuous drainage of the ventricles, a tube was inserted into the enlarged ventricle through the occipital region. An accurate hourly record of the amount of fluid was not obtained; however, the nurse's notes covering several days report "no drainage" in the early morning and toward daybreak, "tube draining well." In the latter case, there was no manipulation of the tube at any time; in the former case, with the hourly record shown in figure 1, every night when the drainage stopped the tube was disconnected, warm Ringer's solution was run through it and fluid aspirated; at times the ventricles were tapped. Blockage of the drainage tube was not found, and there was no increase in the intraventricular pressure. Several hours later, the drainage would begin spontaneously without further adjustment of the tube.

This variation was so striking that the records of several patients in whom periodic drainage had been instituted were studied. The fluid

* From the Surgical Department of the Johns Hopkins University and Hospital.

obtained had been accurately measured and recorded together with the time of the ventricular puncture. This method of drainage is easy and reliable as there is no question of the patency of a tube. Each time the ventricles were drained until all pressure was relieved. Figures 2, 3, 4, 5 and 6 are sections of the charts which were made, all of them showing that in the early morning much less fluid is formed than at other times

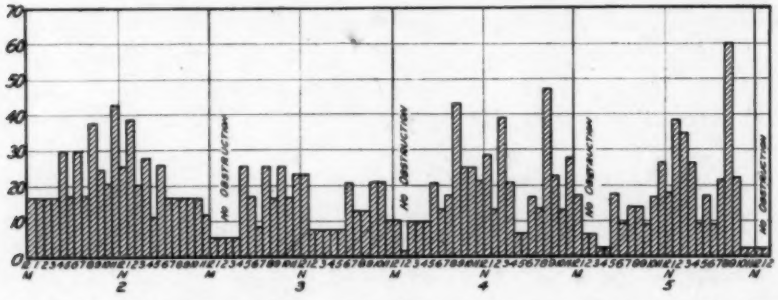

Fig. 1 (case 1).—The hourly record of the drainage of cerebrospinal fluid in a patient having a block about the base of the brain. The chart begins at midnight of the day of operation so the relatively larger amount of drainage for the first few hours might be explained partly as being serum, and partly as a response to the irritation of this foreign substance. The decrease in the amount of drainage for the early morning and afternoon hours is evident. No obstruction indicates the points at which the drainage tube was tested and found to be patent.

In this and the subsequent charts the amount of fluid is indicated in cubic centimeters on the side. The hours are recorded beneath, while midnight is indicated by a double vertical line and *M* at the base, noon by a single vertical line and *N* at the base. Beneath the *N* is given the postoperative day.

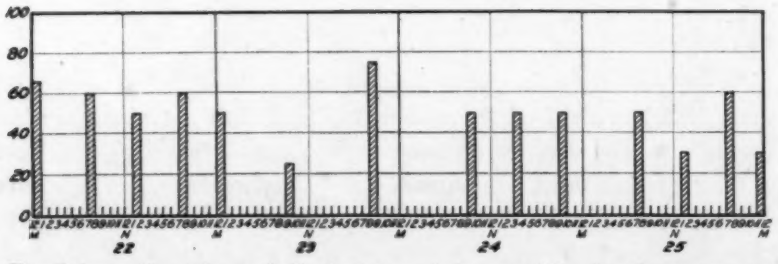

Fig. 2 (case 1).—The periodic drainage of the ventricles for the twenty-second to the twenty-fifth postoperative days. In this and the subsequent charts the hour of the ventricular puncture is recorded at the base, and the amount of fluid, (indicated in cubic centimeters at the side) is given by the height of the column. If the time interval between punctures is considered, it is seen that the least amount of fluid is formed during the early morning hours.

during the day. This is particularly well demonstrated when the ventricular punctures were made around 4 or 5 a. m. (fig. 3); but if the interval of time is considered, it is seen that this is uniformly true. Of course, punctures performed after 8 or 9 a. m. should be discounted, since

the time interval includes part of the period of more profuse drainage or formation of fluid.

A pronounced demonstration of this decreased formation of fluid in the early morning was given by a patient, aged 30, who had a bilateral hydrocephalus caused by a metastatic melanotic sarcoma just over the aqueduct of Sylvius (fig. 7). Every four to six hours during the day he would become progressively drowsy and finally comatose. When the intracranial pressure was relieved by a ventricular tap, he would rouse

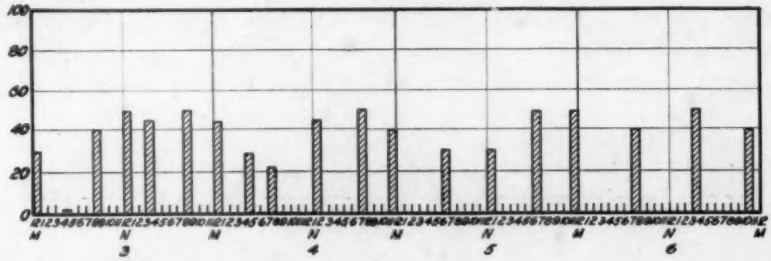

Fig. 3 (case 2).—This chart also shows the decreased amount of fluid in the early morning hours. This is particularly well illustrated on the third and fourth days after operation, when the ventricles were drained between 4 and 5 a. m., and little fluid obtained. The patient drank large quantities of fluids, and each night between 12 and 8 a. m. would take from about one third to one fourth of the total fluid intake for the twenty-four hours.

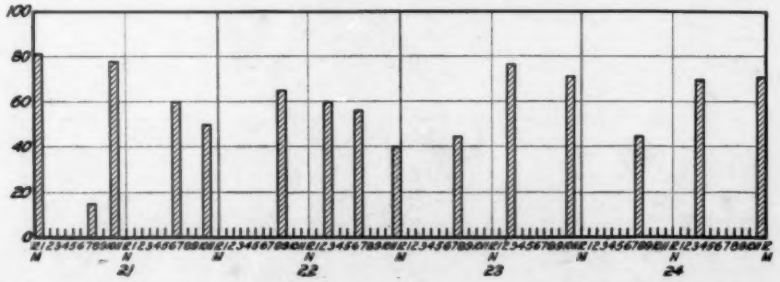

Fig. 4 (case 3).—The periodic drainage of the ventricles in a case of hydrocephalus with a tumor removed from the region of the pineal and third ventricle. The decreased amount of ventricular fluid in the early morning hours is striking; this occurred in a patient who was drowsy, who gave no apparent thought to his surroundings, and who was receiving fluids by gavage, by subpectoral infusion and by rectum. Accordingly, there was little variation in the amount of fluid taken during a given interval of time regardless of whether it was night or day.

and ask for water or food while the fluid was still draining from the needle. He would remain bright for from one to three hours afterward, but it was always necessary to relieve the pressure just before meals were served. However, after from six to nine hours had elapsed at night without ventricular drainage, he would awake in the morning,

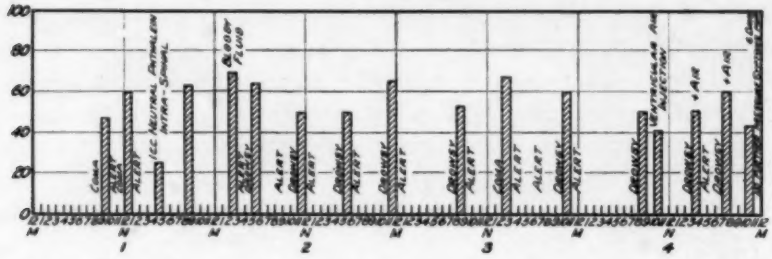

Fig. 5 (case 4).—Besides the variation in the amount of ventricular fluid formed during the day and night, this chart shows the much larger quantity of fluid obtained after intraspinal injection of neutral phthalein and when bloody fluid was present within the ventricles. This reaction, probably mostly due to the presence of the blood, passed away within twenty-four hours. Note also the reaction following the ventricular injection of air with more rapid development of intracranial pressure, the larger volume of air and fluid released from the ventricles and the spontaneous relief from all pressure symptoms for the six days following the injection. This relief was apparently the result of the forcing open of the aqueduct which was closed by a small overlying tumor (fig. 7). The word "drowsy" was used on the chart regardless of whether the patient was drowsy or comatose. In general, the state of consciousness corresponded inversely to the amount of fluid within the ventricles. It was most notable that after a longer period of time at night the patient would waken and eat breakfast before the ventricles were drained, whereas during the day they had to be tapped before each meal.

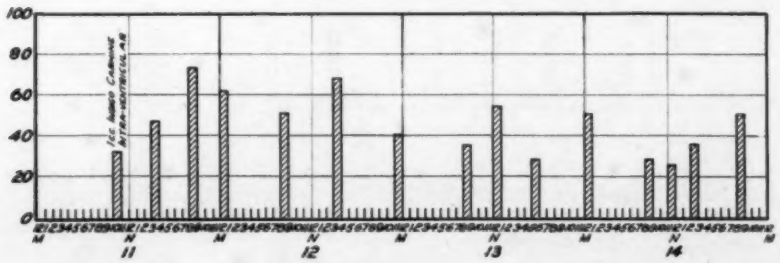

Fig. 6 (case 4).—A continuation of the same case as that represented in figure 5 after the six days of relief from symptoms of increased intracranial pressure. It shows in addition to the variation in the quantity of ventricular fluid from the day to night that there was a considerable increase in the total amount of fluid obtained for the twenty-four hours after the intraventricular injection of indigo carmine. This dye did not pass through to the spinal fluid, indicating a complete block which later at autopsy proved to be at the aqueduct (fig. 7).

cooperate in being prepared for the day, and frequently eat his breakfast before becoming comatose. The punctures made in the morning after this longer period of time were always productive of less fluid than those made during the day, and the patient was never in coma (figs. 5 and 6). Figure 3 is even more striking, showing the results of two punctures performed between 4 and 5 a. m., little fluid being obtained.

There are certain exceptions to this rule of diminution in the amount of drainage during the early morning and afternoon; these cases come under the general classification of some irritating substance within the ventricles. Figures 5 and 6 show the results of injection of air and neutral indigo carmine into the ventricles in such cases. Neutral phenolsulphonphthalein was also injected into the spinal canal (fig. 5), causing

Fig. 7 (case 4).—A cross-section of the brain of patient J. McC. (figs. 5 and 6) with a nodule of metastatic melanotic sarcoma just above the aqueduct. The aqueduct is compressed to a slit, and the temporary opening of this could explain the relief from intracranial pressure following the injection of air (fig. 5).

a marked increase in the amount of ventricular drainage for the following twenty-four hours. This was true when there was a complete block at the aqueduct, as was proved by the fact that the dye did not come through to the ventricles. This could possibly be explained by the secondary pressure exerted on the ventricles by either the extravasation of fluid or the lack of absorption of fluid in the subarachnoid space as a result of the irritating action of the phenolsulphonphthalein. It seems more likely, however, that the blood in the ventricular fluid, as noted in figure 5, was more probably the irritating factor, since it was within the ventricle. Careful study of the record of the case of another patient who failed to show this marked decrease in the amount of fluid at night revealed that he had an intraventricular tumor, and bloody ventricular

fluid was frequently noted. It has been frequently observed that air, neutral phthalein, neutral indigo carmine or blood within the ventricles act as irritants, and their presence demands more frequent tappings for relief from intracranial pressure; this more rapid formation of fluid does not follow the general curve shown in figure 1. The greater part of this irritating action has usually passed away within twenty-four hours.

The irritation from air seems to last longer and be more pronounced than that caused by either the neutral phthalein or by indigo carmine; this is particularly true in the presence of obstructive hydrocephalus. An unexpected exception to this observation was the injection of air as shown in figure 5. Apparently the increased pressure as a result of the irritation of the air forced open the aqueduct and allowed the fluid to reach the subarachnoid space, where it was absorbed (fig. 7). The patient was relieved from symptoms of pressure for six days after the injection, and the actual record of intracranial pressure by ventricular puncture showed that there was no elevation. This can be readily understood by a glance at figure 7, which shows the small metastatic melanotic tumor just over the aqueduct, where it could readily cause temporary blockage to the passage of fluid from the third ventricle.

In all of the patients studied to obtain data for the charts and particularly in the patients in the first four cases which are reported, the presence of a block was determined or proved by one or more of the following methods: (1) by the injection of neutral phthalein, indigo carmine or air; (2) by ascertaining the presence of a bilateral hydrocephalus accompanied by a difference in the color and character of the ventricular and spinal fluid (i.e., amount of blood, globulin, etc.) and (3) by operation or postmortem examination.

In addition, the intracranial pressure would lead one to suspect that a block was present or that there was a marked diminution in the amount of fluid absorbed. When there is complete blocking off of the ventricular system from the subarachnoid space the amount of fluid that can be absorbed is minimal and can be ignored. The amount of fluid obtained by drainage is as near the total amount formed as it is possible to obtain by experimental methods. It seems proved, therefore, that there is a definite and marked variation in the amount of ventricular fluid which is normally formed during different periods of the day and night.

I have no proved explanation of this variation to offer. Every nurse's chart was gone over carefully. The temperature and the pulse and respiration rates did not show any change other than the usual response to increased intracranial pressure.

No correlation could be determined as to the intake and output of fluid. Some of the patients were given nasal feedings late at night; others received the major portion of their fluids by subpectoral infusion

and dextrose by rectum both day and night without variation. The record of one of the patients who was able to take fluid by mouth showed that over a period of eight days there was only one night during which the fluid intake, between midnight and 8 a. m., was less than from one third to one fourth of the total amount taken during the twenty-four hours (fig. 3). When the fluid intake is markedly insufficient, causing body dehydration, there may be a decrease in the amount of the ventricular fluid. An extreme example of this is the case of a man with obstructive hydrocephalus who was brought to the hospital in coma and who was having convulsions every five or eight minutes. Trephine openings had previously been made for diagnostic purposes. The ventricles were tapped, and the intracranial pressure was considerably less than the atmospheric pressure. He was immediately given 800 cc. of 5 per cent dextrose intravenously and a subpectoral infusion of salt, and the administration of 5 per cent dextrose by rectum was started and allowed to run slowly. The convulsions ceased within an hour and a half; a few hours thereafter the ventricles were tapped, and the fluid was found to be under markedly increased pressure. The convulsions did not recur during the remainder of the patient's stay in the hospital.

The only stimulants which had been given to any of the patients were coffee, tea, cocoa, coca cola and cigarets. These showed no demonstrable effect on the amount of drainage.

No relationship could be determined between the state of consciousness and the amount of ventricular fluid. At one time the patient was asleep and at another awake during the periods of decreased drainage. The little girl who would take a third of the total fluid intake for the day between midnight and 8 a. m., and who was frequently asking for water, was awake a great part of the time (fig. 3). It must be kept in mind, of course, that even if the patient was awake, at this time of night there was far less outside stimulation in the form of noises, light and general activity than during the day or evening. This, however, would not explain the less definite drop in the afternoon. Some patients who were always in a stupor showed this variation. The only definite relation between consciousness and the amount of fluid was the drowsiness and stupor secondary to pressure, and these were more pronounced and came on more rapidly during the day or early evening. Headaches and vomiting were sometimes associated with these symptoms. The headaches, however, were as severe when there was a complete reduction of pressure as when there was too much pressure.

It might be thought that the movements of the body would influence the amount of fluid where there was continuous drainage. A careful record of any changes in position, however, fails to show any increase or decrease in the amount of fluid following either voluntary or passive turning.

On looking back over these cases, it seems highly probable that there was a parallel between the blood pressure and the amount of ventricular fluid, but since no simultaneous record was kept, this cannot be proved.

Many possibilities of investigation are suggested. For instance, the following points might be studied: (1) the relation of blood pressure to the amount of ventricular fluid; (2) the relationship of fluid intake and output to intracranial pressure and the formation of ventricular fluid, particularly with reference to low fluid intake; (3) the influence of drugs and stimulation on the amount of fluid, and (4) whether or not at any particular time drugs in the blood stream are more apt to gain access to the ventricular fluid, etc.

SUMMARY

There is a marked variation in the formation of cerebrospinal fluid for the different periods of the day and night. In general, there is a decrease in the amount of fluid in the early morning and afternoon and an increase in the forenoon and evening. The practical cessation in the formation of fluid for the few hours after midnight is most striking.

A considerable number of substances, in general classed as irritants (air, neutral phthalein, neutral indigo carmine, blood, etc.) in the ventricles will give a marked increase in the formation of fluid without regard to the time of day or night, and demand more frequent tapping for relief from pressure.

There is no proved explanation as to why this occurs, but it seems probable that it is related to general vital activities. Possibly it parallels the blood pressure curve. There may be some similarity to the variations in the amount of urinary secretion, but this is not so striking as to show that it is directly influenced by the fluid intake.

REPORT OF CASES

CASE 1.—*History.*—(History obtained from the patient's father, a physician.) W. M., aged 16, complained of disturbance of vision and gait, and projectile vomiting. The onset of the present illness was dated from a fall for a distance of about 4 feet and 2 inches (127 cm.) at the age of 14 months, when the child struck his head. He was unconscious for a few minutes and had a laceration of the head which healed by granulations. Following the injury the patient had a bilateral paralysis which lasted for three weeks, but after six weeks he was thought to be normal. During this time he had attacks of vomiting and cried a great deal. (In later life these attacks of vomiting persisted, and then the patient complained of associated headaches.) When the patient was about 30 months of age, it was noted that there was a paralysis of the extra-ocular muscles on the left side. This cleared up after six months, but after that time there was some weakness of the external recti on both sides.

There was no particular trouble until the patient was 6 years of age, when he was thrown from a horse and was unconscious for an hour. For the two days following he was unable to stand. He had always been clumsy, and the clumsiness increased after this fall. At 8 and also at 12 years of age, the patient

had falls which were severe and which were caused by his clumsiness. When 12 years old, he tripped while running and struck his head. Severe headaches followed for twelve days. He fell again and was found on the lawn turning around and around, always toward the right and complaining of his head; after a short time he fell unconscious. The following day he was unable to walk and remained in bed in a hospital for sixty-one days, with a temperature ranging from 100 to 102.5 F. He was drowsy most of the time and complained much of headache. For the following sixteen days he could walk with support, and then was able to get about alone. His condition was then fairly satisfactory for two years. About two years before presentation, at the age of 14, the headaches again came on and became more constant and more severe. Since then it had been noted that he staggered toward the right. The disturbance of gait and the awkwardness and clumsiness became progressively worse.

In February, 1925, five months prior to presentation, following a cold he became much worse, almost over night. He was unable to walk and fell to the right. He had headaches and projectile vomiting; these symptoms grew progressively worse.

Examination.—The patient was a rather obese white boy, aged 16, who showed no evidence of outdoor life. He had a very large head, and wore a 7¾ hat (hydrocephalus). The cranial nerves showed that there was marked impairment of vision in both eyes, and he was just able to count fingers. There was slight choking of the disks on both sides, more marked on the right. There was a paralysis of the external rectus muscle on the left, and marked nystagmus on looking to either side. The pupils were large and reacted to light. Apparently sensation was normal on both sides of the face, but the corneal reflex was probably a little less acute on the right. A definite facial weakness was present on the right side. Some impairment of hearing was noted on both sides, air conduction being better than bone conduction. Other cranial nerves functioned normally.

Mentally, there seemed to be considerable impairment. There was weakness of the entire right side of the body, though it was thought that this might be due to a cerebellar lesion. Aphasia, hemianopia or uncinate attacks were not noted.

There was a markedly positive Romberg sign, the patient falling to the right; ataxia was more marked on the right, both in the arms and legs; nystagmus was present. Adiadokokinesis was more marked on the right. The reflexes were normal.

First Operation.—June 19, 1925: A cerebellar exploration was performed and a large, thrombosed hemangioma was revealed; the tumor was thought to be inoperable. The wound was closed. The patient made an uneventful recovery.

Second Operation.—June 30, 1925: Cerebellar approach, second stage, was the procedure used this time. The thrombosed hemagioma was partially excised. The temperature rose rapidly; by evening it had reached 106.5 F., at which time it was decided to establish continuous drainage of the cerebellar region for relief from pressure, which recurred rapidly after ventricular puncture.

June 30: The cerebellar wound was explored and a drainage tube inserted. The patient continued to improve during the night and remained conscious; drainage was good, and the temperature gradually fell.

July 1: Drainage was free, 320 cc. for fifteen hours after operation; the fluid intake was 5,000 cc. for twenty-four hours.

July 2: The condition of the patient improved. He took large amounts of fluid by mouth. There was not so much drainage in the early morning; the tube was not obstructed.

July 4: Drainage continued as shown by the chart. The patient was placed on a soft diet, and allowed to smoke. The drainage fluid showed a few organisms (*Staphylococcus albus*), but they apparently gave no reaction. The white blood cell count was 10,000. There was little drainage in the early morning hours.

July 6: Drainage practically ceased after midnight; the tube was patent, and ventricular puncture did not show intracranial pressure.

July 7: There was some leakage around the tube for the first time. The patient was not very responsive and did not use the left side.

July 8: The patient continued to have a temperature up to 104 F. The white blood cell count was 6,200. There was little drainage in the early morning hours and no leaking around the tube. During the past thirty-six hours 450 cc. had been drained.

July 9: The patient continued to have a somewhat high temperature. The drainage tube was removed. The patient took from 5,000 to 8,000 cc. of fluids a day.

July 11: Since the removal of the tube the temperature had been lower; the sinus tract was closed.

July 15: Little change occurred in the patient's condition. Ventricular puncture and the culture of the fluid did not show any organisms or growth.

July 17: The patient continued to be drowsy and listless. Ventricular punctures were made two or three times a day for release of pressure; no organisms were found and the cultures were negative.

July 19: The patient grew progressively worse and became more listless. Ventricular punctures were continued. Fluids were taken well, particularly after a ventricular puncture.

July 22: The condition remained about the same. Frequent ventricular punctures were made. The patient had some distention of the bladder; however, he voided immediately following a ventricular puncture. As the intracranial pressure increased, however, there was no further voiding, and the distention became marked before the next puncture. He took nourishment and fluids well.

Third Operation.—July 22: Frontal trephining was performed for ventricular punctures. The ventricles were drained, and immediately the patient voided 650 cc. of urine.

July 24: The patient continued to be drowsy. There was a rise in temperature. He took less fluid and was becoming progressively worse. Ventricular drainage improved the state of consciousness, but not the temperature curve.

July 28: The patient continued to grow worse until death. The fluid intake was kept up by subpectoral administration of salt and dextrose given by rectum. The chest filled up with mucus. The temperature rose to 108 F., and death followed.

CASE 2.—*History.*—(History obtained from patient and mother.) W. F., aged 6, complained of headaches and failure of vision. The present illness began three months before presentation, since which time the patient had become weaker; she tired easily and complained of frontal headaches. She also became more clumsy. Her vision was blurred, and about a week before admission she apparently became blind in the left eye, and there was marked impairment of vision in the right eye. A lumbar puncture was performed two days before admission to the hospital, and since that time the headaches had been much worse, and the patient had been unable to sit up. She had been restless, and complained of pain in her head. She suffered much with nausea and had a tendency to fall backward.

Examination.—Apparently there was no perception of light in the left eye. The right reacted to light. There were marked bilateral choked disks without hemorrhages. The extra-ocular movements were normal. (No history of diplopia was given.) The remainder of the neurologic examination did not reveal any pathologic conditions, except some disturbance of the visual fields, which were distorted; there was some variation on different examinations. Most of the vision in the left eye was lost, and on the right the visual field was markedly constricted.

Operation.—June 25, 1926: Trephining and ventricular estimation with injection of indigo carmine were performed, which showed a bilateral hydrocephalus with free communication between the two sides.

Second Operation.—June 26: A cerebellar exploration did not reveal any evidence of a tumor. The ventricles were tapped; all the dye had disappeared, though it was present at the time of two punctures during the night. Indigo carmine was then injected into the ventricles, and came through to the fourth ventricle readily. The patient was thought to have some meningeal irritation of a mild character, which caused decreased absorption of fluid and increased pressure.

The patient made an uneventful recovery, with relief from symptoms of pressure; she was discharged eighteen days after operation, much improved.

She was readmitted July 20, four days after discharge. The patient was well for two days after discharge and then had a recurrence of the pressure symptoms. There was marked failure of vision, which had been improving, and headaches and vomiting had recurred. The occipital decompression, which had been soft, bulged markedly.

Third Operation.—July 20: Ventricular estimation was performed, and indigo carmine was injected. The dye passed quickly across the third ventricle. A lumbar puncture was performed, but the dye did not come through to the lumbar canal. After the immediate reaction and relief by ventricular punctures, the patient continued to improve, and did not show any signs of intracranial pressure.

Fourth Operation.—July 30: A ventricular air injection was performed for diagnosis; 60 cc. of fluid was obtained and 45 cc. of air was injected. Roentgenograms were made and an examination of them showed bilateral hydrocephalus, but the two lateral ventricles were constricted on both sides just anterior to the point at which the three horns come together. In the anteroposterior view, the third ventricle was difficult to fill, but after several roentgenograms were taken, it was seen in one. It was broad and seemed somewhat dilated, but the shadow was light, indicating that there was a thin layer of air in this region. This was interpreted as indicating that only the uppermost, that is, when the patient was lying on the back of the head, the most anterior part of the ventricle was filled with air. It was questionable whether the remainder of the ventricle contained fluid or tumor, but since in the usual picture the third ventricle casts as dark a shadow as the lateral ventricles, it was felt that there must be a tumor of the third ventricle. Frequent ventricular punctures were made for the release of intraventricular pressure. The patient's condition remained satisfactory.

Fifth Operation.—July 31: Right craniotomy was performed with the patient in a cerebellar position. The occipital bone flap was removed, the corpus callosum split, and tumor removed from the region of the pineal and third ventricle. The vein of Galen had to be ligated for exposure. Bleeding did not occur after the tumor was removed, and the wound in the head was closed without drainage. The tumor extended into the third ventricle anteriorly, and after the closure, needles

were inserted into each of the lateral ventricles, and the air was removed by gradually filling the ventricular system with warm Ringer's solution. On account of the edema resulting from the operation over the aqueduct, the ventricles were tapped every four hours for the release of pressure, and considerable quantities of fluid under pressure were obtained. This periodic drainage was kept up for several days, and after the immediate effects of the operation began to wear off, the punctures were performed less frequently and finally discontinued, the area of cerebellar decompression being watched for fulness as an indication for ventricular drainage.

The patient was discharged twenty-five days after the last operation, able to walk. The eyes showed optic atrophy and marked impairment of vision. She was able to distinguish objects to which there was some contrast, and she was relieved from all symptoms of intracranial pressure. The cerebellar decompression was soft.

Case 3.—*History.*—(History obtained from father.) W. M., aged 12, dated the onset of the present illness to one year before presentation when he began to have headaches. Six months previously he began to have short attacks of dizziness associated with headaches and nausea. The headaches and vomiting continued with some remissions. One month previously, he became progressively weak and was unable to walk. There was a loss of control of the sphincter. There had not been any noticeable disturbance of vision nor any disturbance of swallowing, but recently, there had been progressively increasing difficulty in speech.

Examination.—The patient was stuporous and did not move; to any question, after about a minute, he would answer "What?" There was weakness of the left internal rectus muscle, choked disk and tortuosity of the vessels on both sides. Facial weakness was noted on the right. Swallowing was apparently normal. Spasticity of the right arm and leg was noted, and sensation was apparently better on the right side. The patient was unable to sit up. The Babinski sign was positive on the right side and questionable on the left. Deep reflexes were hyperactive on the right. The diagnosis was probable cerebellar tumor.

Operation.—June 22, 1926: Trephining and ventricular estimation were performed. After the injection of the indigo carmine, the color did not appear in the opposite ventricle until the fourth aspiration, and then faintly. Both ventricles were dilated tremendously. Even after the twentieth aspiration back and forth the fluid obtained from the right ventricle was much less colored than that on the left, where the dye was injected. On account of this discrepancy, a ventricular injection of air was performed.

One hundred cubic centimeters of fluid was aspirated from the left ventricle and the fluid replaced by air up to 65 cc. The usual series of roentgenograms were taken. These showed marked dilatation of the lateral ventricles and the third ventricle not filled. The air crossed the midline readily. The usual cerebellar exploration was made with cross-bow incision. There was fluid over the surface of the cerebellum and a small cisterna magna; herniation of the cerebellar tonsils had not occurred. The two cerebellar lobes were the same size, and their appearance was normal. Exploration of the cerebellopontile angle on either side and also of the fourth ventricle did not show any evidence of tumor. The floor of the fourth ventricle was scaphoid, so it was thought that there could not be a tumor of the underlying tissue of the brain. The pineal shadow suggested that there must be a tumor in that region, and accordingly the wound was closed. The patient made a fairly rapid recovery. Several ventricular punctures were

made each day to keep down the intracranial pressure. Thirteen days after operation, the patient vomited; he did this on several of the following days. This condition, as well as the state of consciousness, was improved by frequent ventricular tappings. Improvement soon ceased, and several ventricular punctures a day were required for the relief from pressure; cultures of the ventricular fluid were negative for organisms, and twenty days after operation the patient was thought to be in condition for a craniotomy for exploration of the pineal region.

Second Operation.—July 16, 1926: Right craniotomy was performed for pineal approach. A tumor in the pineal region and extending into the third ventricle was removed.

With the patient in the cerebellar position, a small flap was turned down, well posteriorly; the veins leading into the sinus were doubly ligated and divided, allowing the right cortex to fall away from the midline. The corpus callosum was exposed and divided for about 4 cm. The vein of Galen was ligated doubly and divided. The tumor was then dissected free, and all bleeding was controlled. The tumor was definitely circumscribed and projected into the third ventricle. After removal of the tumor, the operator could see most of the third ventricle.

The patient made a slow recovery, and frequent tappings were necessary for relief from pressure. For ten days following the operation he continued to have a temperature as high as 103 F., but without evidence of infection in the ventricular fluid.

Third Operation.—July 27, 1926: Trephining was performed for ventricular puncture because of local irritation about the trephine openings which had been in almost continuous use for over a month, and it was feared there would soon be danger of the infection being carried into the ventricles.

The patient lived for fourteen days following the last operation. At first he did not improve, and then he became progressively worse and more stuporous. The chest became more filled with mucus; the temperature rose and the pulse rate became rapid. Cultures of the ventricular fluid were negative up to the time of death. Autopsy revealed the aqueduct plugged with blood clot.

Case 4.—*History.*—(History obtained from wife and father, a physician.) W. M., aged 31, complained of headaches and disturbance of vision. The present illness dated to two months before admission, when he began to have headaches and diplopia and to vomit. There were several operations on, and irrigations of, the air sinuses about the nose. It was thought that there was some improvement for a short time. His condition became worse, and was accompanied by dizziness, choked disk, headaches and vomiting. A staggering gait was noted, and there was some occipital soreness. At times it had been difficult to arouse him. Otherwise his history was negative.

Examination.—The results of the neurologic examination were negative except that considerable impairment of vision was found without restriction of the visual fields, marked choking of the optic disks, old and recent hemorrhages in the eyegrounds, with enlargement and tortuosity of the vessels. There was slight weakness of the superior rectus muscle on the left, and also some weakness of the external rectus muscle on this side. There was no nystagmus, but the patient was unsteady on his feet, and his gait was staggering. The impression was that there was a tumor of the brain of undetermined location.

Operation.—Nov. 27, 1925: Trephining and ventricular estimation were performed. The usual occipital trephine openings were made; both ventricles were tapped and found to be dilated, with the fluid under increased pressure. One cubic centimeter of neutral indigo carmine was injected and passed rapidly over

to the opposite side, indicating that there was a block posterior to the third ventricle.

A cerebellar exploration was made, but a tumor was not located. The patient made an uneventful recovery from anesthesia. The temperature rose to 103. Ventricular punctures were performed about once a day, but only a moderate increase occurred in the pressure. The patient remained conscious and recognized his family.

December 6: There had been a marked change in the patient's condition within the past two days. He frequently became drowsy but was relieved by ventricular punctures, large quantities of fluid being withdrawn, and under fairly high pressure. At times it was necessary to drain the ventricles as often as every three or four hours. He received immediate relief from pressure with the drainage of the ventricles. He voided voluntarily, and ate fairly well. The respiratory rate was slow at times in accordance with the pressure. Lumbar puncture was performed with the injection of 1 cc. of neutral phthalein in the lumbar spinal canal. None came through to the ventricular fluid over a period of twenty-four hours. The fluid from the spinal canal was definitely yellow, probably as a result of the recent cerebellar operation, while the fluid from the ventricles was more bloody and was not yellow. The total amount of ventricular fluid obtained during the day was 148 cc.

December 7: The condition remained about the same. It was necessary to puncture the ventricles frequently, five times during twenty-four hours, and a total of 299 cc. of ventricular fluid was withdrawn. This increased quantity was thought to be due either to the bloody fluid in the ventricles or possibly to the injections of phthalein, though this did not come through to the ventricles.

December 8: There was little change in the condition of the patient; the punctures were not so frequent; only three were performed, 180 cc. of fluid being released. It was noticeable that the patient did not show evidence of pressure during the night, but that early in the morning after the secretion of the fluid became more rapid, there was a rise in the pressure. Immediately following the release of the fluid, the patient became talkative and more alert mentally. He voided continently at times. Puncture was not performed between 11 p. m. and 8:30 a. m.; at the morning puncture there was only moderate pressure, and only 53 cc. of fluid was obtained. The usual amount was from 60 to 75 cc. for shorter periods of time. When the next puncture was performed at 1:30 p. m., after an interval of only five hours, the pressure was greater, and 68 cc. of fluid was obtained.

December 9: Little change was noted in the condition, but it was again noticeable that the patient did not develop signs of pressure throughout the night. Ventricular puncture was not performed between 10:30 p. m. and 8 a. m., and the patient was just becoming drowsy when the fluid was drained. Only 50 cc. was obtained.

It should be noted that whenever there was pressure there was a marked increase in the deafness, even if the patient was still able to talk. There was no diminution in the associated corneal reflex. The patient was sent to the operating room for ventricular injection of air, so that before the pineal region was explored it might be ascertained that there was no cortical tumor.

Second Operation.—Dec. 9, 1925: The right ventricle was tapped, and 100 cc. of fluid was aspirated and replaced with 75 cc. of air. The roentgenograms showed that the ventricular system was uniformly dilated throughout, including the third ventricle, and that no distortion was present. No air reached the subarachnoid space within half an hour following the injection.

The air was released from the ventricles on two occasions at short intervals and with considerable increase in the intraventricular pressure. Throughout the remainder of the day, the patient seemed brighter than before the injection of air. The ventricles were tapped on two occasions during the evening, and it was expected that they would have to be tapped during the night.

December 10: The patient remained clear mentally, and did not show any symptoms of pressure. When the ventricles were tapped in the morning only 38 cc. of fluid was obtained, and it was not under marked pressure. The patient was conscious, and was better than at any time during the preceding ten days. During the remainder of the day, he was bright and talkative, and said that he could see better. The disturbance of the extra-ocular muscles was not so great, and he seemed to be generally improved.

December 12: The patient continued to improve. Further punctures were not made. Headaches did not occur and the patient could hear better, which was determined by the audiometer. He did not like to be disturbed, however, and lay quiet except when it was necessary for him to move.

December 15: The patient's condition had been growing progressively worse for the past three days. He was listless, and frequently would not respond, though he was able to talk when he desired. The ventricle was tapped on the previous day; only 28 cc. of fluid was obtained, and this was under moderate pressure. The left ventricle was tapped, and fluid was obtained under moderate pressure. One ampule of neutral indigo carmine was injected, and four hours later a lumbar puncture was performed, but there was no evidence of dye in the fluid obtained. The ventricle was then punctured; the dye was obtained in concentrated form. The fluid was under more marked pressure, and there was a little rise in the temperature up to 101.5 F. following the injection of the dye.

December 18: In order to obtain relief from the intracranial pressure, it was necessary to puncture the ventricles frequently after the injection of the indigo carmine.

It was learned that about a year previous to presentation the patient had had a pigmented tumor removed with radium from the sole of the left foot. This was done because the tumor had become ulcerated. There were some moderately enlarged lymph glands in the groin. One of these was to be excised on December 18, since it was thought that the whole picture might be due to metastatic melanotic sarcoma.

Third Operation.—December 18: The lymph gland in the left groin was excised for diagnosis. Grossly, the glands were replaced by a black, pigmented growth. The pathologist reported a metastatic melanotic sarcoma of the left inguinal gland.

Punctures were not made after the last operation, although nourishment and general nursing care was continued. The patient died after seven days.

December 25: Autopsy revealed metastases of the melanotic tumor to the left inguinal glands with extension into the femoral vein, retroperitoneal tissues, suprarenals, thyroid, thymus, brain, heart and bone marrow of the left femur.

EFFECT OF MERCUROCHROME-220 SOLUBLE ON THE GROWTH OF BACILLUS PYOCYANEUS*

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The work described in this article was undertaken following the observation in a neighboring hospital that *B. pyocyaneus* was found, in several contemporary cases, growing in dressings of mercurochrome-220 soluble after the first twenty-four hours' applications to a wound. The questions arising for solution concerned the unusual frequency of infections by *B. pyocyaneus—Pseudomonas aeruginosa* (Schroeter)—usually an infrequent invader, and the specific value of mercurochrome as an antiseptic in infections with this microbe.

Pus was chosen as a medium for growth in an endeavor to imitate to some degree the conditions in the body, especially in infected surgical incisions. The pus used was sterile, having been drawn from a shoulder bursitis and having failed to produce any growth on blood agar plates or in dextrose broth. It was thick and creamy and on microscopic examination showed countless pus cells and ropey, mucus-like shreds, but no bacteria.

The cultures of *B. pyocyaneus* and *Staphylococcus aureus* used were fresh twenty-four-hour growths from plain agar slants. The characteristic coloring of *B. pyocyaneus* when grown in air made the readings extremely easy and definite.

The mercurochrome was the standard 2 per cent solution obtained from a freshly prepared stock supply on one of the surgical wards here. The iodine was the standard tincture of iodine.

EXPERIMENTS

The following experiments were performed:

Experiment 1.—Tube 1, containing 2 cc. of sterile pus, was inoculated with one loop of culture of *Bacillus pyocyaneus*, well mixed. Then 2 cc. of a 2 per cent solution of mercurochrome was added as a separate layer without mixing, and the tube was placed at 37 C.

After twenty-four hours, one loop of pus from tube 1 was transferred to agar slant, tube 1 *a*, and this was incubated along with the original tube 1.

After another twenty-four hours, tube 1 *a* showed confluent growth of *B. pyocyaneus*, apparently equal to that in control tube 2 *a* below. Tube 1 *a* was then discarded. In tube 1 the mercurochrome was then thoroughly mixed with the pus, and this tube was continued at 37 C.

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On the next day, one loop of the mixed material from this tube 1 was transfered to agar slant, tube 1 *b*, which showed a moderately heavy growth of the organism in another twenty-four hours.

In this experiment, therefore, the bacillus of green pus grew in pus while the latter was exposed to an equal volume of 2 per cent mercurochrome in a layer over it for forty-eight hours and survived during subsequent exposure for twenty-four hours in the pus mixed with this equal volume of 2 per cent mercurochrome.

Experiment 2.—Tube 2, containing 2 cc. of sterile pus, was inoculated with one loop of culture of *B. pyocyaneus*, well mixed and incubated at 37 C.

After twenty-four hours, one loop of pus from tube 2 was transferred to agar slant, tube 2 *a*, which was then incubated. Two cubic centimeters of mercurochrome was placed over the pus in tube 2, without mixing, and tube 2 was then reincubated.

On the third day, tube 2 *a* showed a confluent growth of *B. pyocyaneus*. This was a control on tube 1 *a*. Mercurochrome was then run in tube 2 *a*, covering the growth completely. At the same time the mercurochrome in tube 2 was well mixed with the pus.

On the fourth day, the mercurochrome was poured off tube 2 *a*, and a loopful of the growth, which had been covered with the antiseptic for twenty-four hours, was transplanted to a fresh slant, 2 *ax*, which was then incubated. Tube 2 *a* was reincubated after the surface of the slant had been rinsed once with distilled water. A loop of pus from tube 2, which had been mixed well with mercurochrome for twenty-four hours, was transplanted to an agar slant 2 *b*.

On the fifth day, tube 2 *ax* showed a confluent and moderate growth. Tube 2 *a* did not show a regrowth; no fresh colonies were found. Tube 2 *b* showed a slightly heavier growth than 1 *b* (experiment 1).

In this experiment, which acted as a control for the growth in experiment 1, the B. *pyocyaneus* was allowed to grow free from the presence of mercurochrome for twenty-four hours. The later addition and mixing of mercurochrome as in experiment 1 did not prevent the survival of *B. pyocyaneus*.

Furthermore, the covering of a growth of this organism on an agar slant with mercurochrome for twenty-four hours failed to prevent successful and free transplantation to another tube with subsequent good growth. This experiment was performed with *B. pyocyaneus* from three sources with identical results. The failure of growth on slant 2 *a* after mercurochrome was poured off was evidently due to exhaustion of the medium and to accumulated products of bacterial growth in the medium.

Experiment 3.—Tube *A*, containing 2 cc. of sterile pus, was inoculated with one loopful of a culture of *B. pyocyaneus*, well mixed. Two cubic centimeters of tincture of iodine was then added as a separate layer without mixing, and the tube was incubated at 37 C.

The second day, a loopful of pus was taken from the bottom tube *A* and planted on an agar slant *A-a*, which was incubated. The iodine was then mixed thoroughly throughout the pus in tube *A*, and that tube was reincubated. The third day tube *A-a* showed no growth. It was reincubated. A loop of pus was transplanted from tube *A* to agar slant *A-b*, which was incubated. On the fourth day neither tube *A-a* nor tube *A-b* showed growth. Because of the possibility of unsuccessful transplantation of *B. pyocyaneus* in the first step, the experiment was repeated a second and a third time with precisely the same results.

This experiment shows, therefore that *B. pyocyaneus* did not survive in pus, in the presence of the standard tincture of iodine, when added either as a layer on the surface of the pus or mixed throughout.

Experiment 4.—Tube *B*, containing 2 cc. of sterile pus, was inoculated with a loopful of a culture of *Staphylococcus aureus* and incubated at 37 C.

The second day, a loop was transplanted from tube *B* to agar slant *B-a*, which was then incubated. Two cubic centimeters of mercurochrome was added to tube *B* and mixed well. Tube *B* was reincubated.

On the third day, slant *B-a* showed a profuse growth of *Staphylococus aureus*. This was a control tube. A loop was transplanted from tube *B* to agar slant *B-b*, which was then incubated.

On the fourth day, tube *B-b* showed no growth. This experiment showed that mercurochrome prevented the survival of *Staphylococus aureus* when it was mixed throughout a medium of pus for twenty-four hours.

Experiment 5.—Tube *C*, containing 2 cc. of sterile pus, was inoculated with a loopful of a culture of *Staphylococcus aureus*, mixed well, and 2 cc. of tincture of iodine was poured on the surface but not mixed. It was then placed at 37 C.

On the second day, a loopful of pus from the bottom of the tube was transplanted to agar slant *C-a*, which was incubated. The iodine was then stirred to mix it well throughout the contents of tube *C*.

On the third day, tube *C-a* showed a sparse growth, a few colonies of *Staphylococcus aureus*. A loopful was transplanted from tube *C* to agar slant *C-b*, which was incubated.

On the fourth day, tube *C-b* showed no growth.

This experiment showed that *Staphylococcus aureus* may survive in pus after the addition of iodine carefully run on the surface of the pus, but that this organism did not survive for twenty-four hours after the mixing of the antiseptic throughout.

Experiment 6.—Tube *X*, containing 2 cc. of 2 per cent mercurochrome, was inoculated with one loopful of a culture of *B. pyocyaneus* and incubated at 37 C. After twenty-four hours, a loop of mercurochrome from tube *X* was transplanted to agar slant *X-a*, which was incubated. Examination of slant *X-a* on the third and fourth days showed no growth.

This experiment showed that *B. pyocyaneus* did not survive in the pure solution of mercurochrome.

Experiment 7.—Tube *Y*, containing 2 cc. of tincture of iodine, was inoculated with one loopful of culture of *B. pyocyaneus* and placed at 37 C. On the second day, a loop of the iodine from tube *Y* was transplanted to agar slant *Y-a*, which was incubated. Examination of slant *Y-a* on the third and fourth days showed no growth.

This experiment showed that the *B. pyocyaneus* did not grow or survive in tincture of iodine.

Both Young [1] and Todd [2] have reported the testing of solutions of mercurochrome against *B. pyocyaneus*, using emulsions of the living organisms. Young's experiments showed this microbe to be somewhat more resistant to the antiseptic than were *B. coli* or *Staphylococcus*

1. Young, H. H.; White, E. C.; Hill, J. H., and Davis, D. M.: A Further Discussion of Germicides and Presentation of a New Germicide—Meroxyl, Surg. Gynec. Obst. **36**:508 (May) 1923.

2. Todd, A. T.: Experimental and Clinical Investigations of Mercurochrome, Lancet **2**:1017 (Nov. 14) 1925.

aureus. Todd found that the bacilli of green pus were easily killed by mercurochrome if very few were present, but if larger amounts of the emulsion of organisms were added, the bacilli survived. He attempted to explain this result on the basis of the presence of increased amount of bacterial protein.

In the present experiments the tests have been made under conditions more nearly simulating body environment, namely, in the presence of pus at body temperature, with exposure to the antiseptics over longer periods of time.

It is evident that mercurochrome has little, if any specific antiseptic action on *B. pyocyaneus* in pus, even when allowed full and complete access to the growth over twenty-four or even forty-eight hours.

Cultures of *B. pyocyaneus* have been isolated from the urine of three patients here within two months. Each of these specimens of urine showed large numbers of pus cells. The use of mercurochrome intravenously, as recommended for pyelitis by some physicians would appear ill-advised in such cases.

One might hazard a guess that the several concurrent infections of this organism, mentioned earlier in this paper, might be due to the fact that an antiseptic was being used which was of practically no value as a weapon against the bacillus of green pus. Such a situation gives rise to a false sense of securtiy. The slightest defects in asepsis of technic might conceivably result in the carrying of the infection from one patient to another, which would have passed unnoticed in the presence of an effective antiseptic.

CONCLUSIONS

1. Mercurochrome is of little or no value as an antiseptic against *B. pyocyaneus*, in the presence of pus or other mediums suitable for its growth.

2. Mercurochrome has practically no effect on *B. pyocyaneus* in pus or on agar even when this organism is exposed freely to large quantities of the antiseptic for many hours.

3. Iodine will effectively destroy *B. pyocyaneus* under like experimental conditions.

4. Both mercurochrome and iodine destroy *Staphylococcus aureus* under like conditions.

5. *B. pyocyaneus* will not grow in pure solutions of mercurochrome or iodine without the presence of another medium.

A REVIEW OF UROLOGIC SURGERY

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(Concluded from page 828)

EXTERNAL GENITALIA

Meyer [52] reviewed the work of replacing undescended testicles and reported a series of cases in which operation was performed by Torek's method. Many hypotheses have been advanced concerning the etiology of undescended and ectopic testicle, the most important of which concern the function of the chorda gubernaculi, the length of the spermatic vessels, the size of the inguinal canal, the size of the scrotum and the prenatal posture.

Histologic examination showed that spermatogenic cells are present and function in about 10 per cent of all cases. The interstitial cells, which have to do with the development of the secondary sexual characteristics, are always abundantly present. Such conditions are almost constant, and therefore the undescended testicles should always be saved.

Secondary complications occur. Malignant degeneration is not as common as is generally believed, and fear of it is not an indication for orchidectomy. Chronic inflammation, the presence of a potential or real concomitant hernia, practically always present, torsion of the spermatic cord and strangulation of the testicle are so frequent that surgical intervention is always indicated.

The best time to operate is before puberty, between the ages of 8 and 10 years if the undescended testicle is unilateral, and earlier if bilateral. The method described places the testicle where it is free from undue trauma, and gives it the best chance to develop, grow and function.

The usual incision in carrying out Torek's method of orchiopexy is like that in operation for hernia. The aponeurosis of the external

52. Meyer, H. W.: Undescended Testicle, Surg. Gynec. Obst. **44**:53, 1927.

oblique is opened. The testicle, which lies in the inguinal canal, is freed and an incision made in the cremaster muscle parallel to the cord. The cord structures are separated out and the hernial sac is then isolated, ligated and resected. All fascial strands and adhesions are freed, which allows the testicle to be brought down to a proper level. An oblique incision is then made in the thigh at about the region of the entrance of the long saphenous vein. A similar incision is made in the scrotum and the posterior lips of the two incisions are sutured. A hemostat is passed upward through the scrotum into the inguinal wound and the testicle grasped and brought down into the thigh-scrotum wound. The testicle is then sutured to the fascia lata and the anterior portion of the thigh-scrotum wound closed. The hernia is then repaired. The second stage of the operation is performed from four to six months after the first; the scrotum is separated from its attachment to the thigh and the testicle dissected from the fascia lata. The skin of the scrotum is then closed over the testicle.

Sixty-four operations were performed on forty-nine patients by Torek's method. Fifteen patients had bilateral, and thirty-four unilateral, undescended testicles. Results were traced in thirty-five cases, and in all the testicles were satisfactorily situated in the bottom of a well formed scrotal sac. In no instance had the testicle atrophied or retracted against the pubic bone or come to lie in the upper portion of the scrotum. In the nine bilateral operations, the results were as good as in the unilateral. Three patients who had bilateral undescended testicles have married since operation and have led perfectly normal sexual lives. Two of the patients have not had children, but the third had a normal child eight years after marriage. Thirty-one operations were performed on patients before or at puberty, and thirty-three were performed after puberty. Of the operations performed on patients after puberty, Meyer has been able to follow the result in thirteen. The results have all been as satisfactory as in operations before puberty.

Thomas and Birdsall,[53] supplementing their previous work on the relative merits of vasopuncture and vasotomy, reported experimental studies. Vasotomy was performed twenty times on ten dogs and vasopuncture twenty times on another group of ten dogs. In eighteen of the first series the vas operated on was occluded in 55 per cent, and both vasa were occluded in 33 per cent. In the series of twenty vasopunctures there was only one occlusion (5 per cent of the vasa operated on). Colloidal silver in a strength of 5 or 10 per cent is a safe antiseptic to use in the vas, providing there is no extravasation

53. Thomas, B. A., and Birdsall, J. C.: Vaso-Puncture Versus Vasotomy Relative to Stricture Formation. An Experimental Study on Dogs, J. Urol. **16:** 529, 1926.

into the spermatic cord. Vasotomy, employing colloidal silver in a strength of 5 or 10 per cent, should be performed with great caution, as traumatism to the vas, and subsequent regurgitation and infiltration of the drug into the spermatic cord causes occlusion in over 50 per cent of operations.

Luys [54] stated that the seminal vesicles may be washed either urethroscopically or surgically. Washing the vesicles through the ejaculatory duct is difficult. The surgical technic is as follows: A cutaneous incision is made at the root of the scrotum about 3 cm. long, the fat is then separated and the cord is lifted; the vas deferens is well isolated from its surrounding connective tissue for a distance of from 1 to 2 cm.; a fine cannula is introduced into the canal; about 10 to 15 cc. of 5 per cent colloidal silver is injected. The wound is closed round a small drain. The patient should stay in bed for at least a week, on a light diet, and remain quiet for at least four days, since the colloidal silver remains in the seminal vesicles for this length of time. Luys claims that his results have been good.

Hepburn [55] described an ingenious treatment for prolapse of the urethra in women. A median line suprapubic incision is made and the neck of the bladder is freed by blunt dissection. The urethra becomes prolapsed because of the poor attachment of the neck of the bladder to surrounding structures. When the finger is run down in the prevesical space, the neck of the bladder separates down to the urethra with little resistance or bleeding.

The hernia or prolapse of the urethra is reduced by traction on a suture in the dome of the bladder. In this drawn-up position, the anterior wall of the bladder is sutured to the structures in front of it, usually to the periosteum of the pubic bone and the posterior fascia of the rectus muscle. The legs must be apart so that an assistant can report when the prolapse is reduced, and whether it stays reduced after the stitches are placed. A rubber tissue drain is inserted to the prevesical space, and the wound is closed around it.

Verriotis and Defrise [56] stated that there is no definite basis for attributing the formation of congenital diverticulum of the female urethra to remnants of the wolffian body or from embryonic proliferation of the urethral wall. They classify these conditions as follows: (1) urethrocele, due perhaps to weakly developed portions of the urethral wall, especially in old age, or to extra-urethral trauma such as

54. Luys, Georges: Technique de lavage des vesicules seminales, Paris chirurg. **18**:207, 1926.

55. Hepburn, T. N.: Prolapse of the Urethra in Female Children, Surg. Gynec. Obst. **44**:400, 1927.

56. Verriotis, T., and Defrise, A.: Des diverticules uretraux chez la femme, J. d'urol. méd. et chir. **21**:97, 1926.

injuries at birth, or endo-urethral trauma such as the passage of a calculus, introduction of foreign bodies or attempts at catheterization; (2) urinary pockets caused by inflammatory processes in the peri-urethral glands, and (3) cysts in the urethrovaginal septum. The symptoms are frequency, dysuria and dribbling. Diagnosis is made by noting the bulging of the vaginal wall, varying in size from 1 to 5 cm. in diameter. Palpation reveals a soft tumor, which on pressure empties into the urethra. Occasionally there may be slight incrustation. For further examination, probing, urethroscopy and roentgen ray may be used. A case is cited of a primipara, aged 35, who six months after difficult delivery manifested the signs and symptoms mentioned. Urethroscopy and roentgenograms revealed an "egg-sized" diverticulum, its orifices 2 cm. from the meatus. The diverticulum was excised; the patient recovered.

[ED. NOTE.—Bumpus gives the following classification of urethral diverticula:

A. Congenital diverticula
B. Acquired diverticula
  (1) From dilatation of urethra from
    (*a*) Calculus
    (*b*) Stricture
  (2) With perforation of urethra from
    (*a*) Injuries to the urethra
    (*b*) Rupture of abscesses into the urethra.
    (*c*) Rupture of cysts into the urethra.

In the male, diverticula of the posterior urethra are generally of the acquired type. Bumpus states that the most frequent etiologic factor is a previous perineal operation. Since urethral diverticula may be associated with a normal bladder they may be easily overlooked unless the posterior urethra is carefully examined.]

Glöckler and Rovinzkij [57] cited a case of urethral fibrosarcoma in a baby girl, aged 13 months. Other complications made it impossible to operate on the tumor. Necropsy did not reveal metastasis. There were no adhesions or infiltration to the adjacent tissue. These facts suggested that operation, if attempted, might have been successful. Microscopically, the tumor was a fibrosarcoma. The authors stated that they have not been able to find a similar case described in the literature at such an early age.

[ED. NOTE.—Fibrous tumors of the urethra are rare at any age, especially in infancy. Benign fibromas or fibromyomas occur more often in the female urethra than in the male. In the female, they may be attached to any part of the urethra but usually to the posterior half.

57. Glöckler, N. E., and Rovinskij, W. P.: Ein Fall von Fibrosarcoma urethrae bei einem 13 monatigen Mädchen, abstr., Ztschr. f. urol. Chir. **20**:464, 1926.

They are generally covered with urethral mucosa, are small and cause few symptoms. The benign tumors may grow rapidly and become very large. If they are large they are usually attached to the urethra by a pedicle, they are not attached to the periurethral tissues and shell out readily at operation. Malignant fibroma usually spreads rapidly and involves the surrounding tissues to such an extent that it may be impossible to determine its original site.]

Besley [58] reported a simple operation for traumatic rupture of the urethra in the male. A sound is passed down to the lacerated portion of the urethra, and logitudinal incision is made in the median line of the perineum, passing through skin and fascia until the bare end of the sound is well exposed, and the lacerated portion of the urethra can be seen.

After a free incision is made which exposes the torn urethra, a large rubber drainage tube is sutured into the wound down to the lacerated urethra. This provides for the escape of urine. The wound is then loosely packed with gauze; this is removed the following day and is not renewed. Six patients have been treated by this method without complication and with rapid convalescence.

Russell [59] pointed out that dilatation, although the accepted procedure for urethral stricture, is inadequate and unsatisfactory. He further pointed out that the urethra possesses two special attributes which make it suitable for excision of strictures: the capacity for spontaneous restoration after it has been slit up, no matter to what extent, and the elasticity or extensibility, which is physiologically controlled, and which enables the urethra to lengthen and shorten in response to changing conditions of the generative organs. This capacity for repair is described as follows:

> The urethra when slit up is converted from a tube lined with mucous membrane into a "riband" covered with mucous membrane; its restoration is to be left entirely to natural processes, and will depend upon the obvious fact that a strip of mucous membrane flanked on either side by raw tissues, which tend naturally to fall together and cohere, will, when this has taken place, be of necessity converted into a tube.

Russell described an operation for excision of strictures which for several years has proved successful in his hands. The steps of the operation with the patient in the extreme lithotomy position, are as follows:

1. The angular incision is made, the apex being over the central point of the perineum. The deep fascia of the ischiorectal fossa is opened on both sides with

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58. Besley, F. A.: Operation for Traumatic Rupture of Urethra in the Male, Surg. Gynec. Obst. **44**:372, 1927.

59. Russell, R. H.: The Radical Operation for Urethral Stricture, Brit. J. Surg. **14**:250, 1926.

a blunt instrument; the left thumb and forefinger are introduced so as to grasp the front portion of the external sphincter. This muscle is severed from its attachment to the bulbocavernosus muscle at the central point and pushed backward. (The new method now diverges from the old, in which the next step conserved the membranous urethra.)

2. The mesial perineal incision is made which exposes the bulb and several inches of the corpus spongiosum and urethra, but without yet opening the urethra. The inflammatory mass comprising the stricture is defined by dissecting it on either side so as to loosen it in its bed, thus making it easy to lift it en masse when the proper moment arrives.

3. A full-sized straight metal bougie is passed down to the face of the stricture; clearly the whole of the urethra now occupied by the bougie is in good order and must be preserved. A transverse cut into the urethra over the point of the bougie is made, the bougie withdrawn, and the transverse cut continued until the urethra is entirely severed (in all its coats) immediately in front of the stricture. The sound urethra is entirely detached from the inflammatory mass. During this step some slitting of the sound urethra may be done if the surgeon desires.

4. The inflammatory mass is dissected out of its bed on the triangular ligament, from before backward and laterally. As it becomes loosened it is turned over backward so that the dorsal aspect of it, with the urethra, the urethral foramen in the triangular ligament, and the face of the triangular ligament itself, all come into view. The most distal portion of the mass, where the stricture must be, is now nearest to the surgeon; on the upper aspect of the mass the urethra will be seen emerging from its foramen in the triangular ligament, to lie more or less embedded on the surface of the mass for a little distance, before it is plunged into the site of the stricture.

5. Removal of the stricture and the inflammatory mass with the minimal length of the urethra. The stricture must be situated at the distal end of the mass, and it must lie between the distal end (previously called the face of the stricture when in situ) and the point at which the urethra is seen entering the mass on its dorsal surface. By a series of sections about 0.6 cm. thick, the distal end of the mass is cut away until the open mouth of the urethra appears, with perhaps a little urine flowing from it; a full-sized rubber catheter is passed through it into the bladder, thus proving that the stricture has been entirely removed. The remainder of the inflammatory mass is clipped away with knife and scissors, and perfectly sound proximal and distal urethras are brought together across an intervening gap that looks wide, but in reality is trivial in extent.

6. Both the proximal and (if not already done) the distal portion of the urethra are now freely slit up, so that the interior of the canal it displayed, being converted into a riband instead of a tube. The ends of the riband are sutured together with fine chromic catgut the knots being on the mucous surface and eventually inside the urethra. In passing the sutures care must be taken to include a substantial share of the external coats of the urethra and corpus spongiosum. A good plan is to put one or two relaxation sutures in the outer coats. A rubber catheter is passed into the bladder and fastened with a suture to the skin; one catgut stitch passes through the skin on both sides at the level of the central point of the perineum, and takes up also the anterior end of the triangular flap, thus bringing it into its proper position. A suitable dressing is applied.

When the patient is returned to bed, a rubber tube is attached to the catheter, and the urine is conducted to a bottle suspended from the side of the bed. Each morning when the dressing is changed the bladder and catheter are gently washed through with boracic acid solution. The catheter is removed on the fifth day, and complete healing of the perineal wound rapidly takes place. Frequently the urine passes almost entirely through the penis during the first twenty-four hours after removal of the catheter.

Duvergey and Dax [60] reported hematuria in six cases of stricture of the urethra. In none was a general cause found for the loss of blood, and it was decided that the condition was entirely local. The authors stated that the urethra itself could not give rise to such severe hematuria. Operative and cystoscopic control proved that the bleeding came from above the urethra.

Two conditions are essential to the production of hemorrhage in cases of stricture of the urethra: congestion and infection. The diagnosis of the origin of such hematuria is important because if it is determined that it is due to the urethral stricture a good prognosis may be given, as the bleeding always disappears with the removal of the urethral obstruction. The treatment consists merely in dilating the stricture and reducing the infection of the bladder by lavage.

Demel [61] described a case of varix formation in the anterior urethra of a boy, aged 14 years. Urethral bleeding was noticed following injury. Repetition of hemorrhage occurred at night and spontaneous bleeding might be seen at any time; the first urine passed was never tinged with blood. Cystoscopic examination was negative. Endoscopy revealed a papillary growth with a smooth surface in the anterior portion of the urethra, 8 cm. from the meatus. This was destroyed with the galvanocautery. A review of the literature revealed six similar cases with the site of the tumor similar to that in his case. Treatment may be carried out with galvanocautery, electrolysis, epinephrine or radium.

[Ed. Note.—These small growths that bleed so freely are not infrequently angiomatous in type. Only a few cases are reported and undoubtedly, as Rokitansky believes, are more representative of simple hypertrophy of vascular segments than of neoplastic overgrowth. They cause little pain or urinary discomfort, and in most cases respond readily to fulguration.

Polyps and papillomas of the urethra are often seen. The majority are minute and are usually the result of long-standing urethral infection. They have little clinical significance. In most cases they disappear

60. Duvergey, J., and Dax, L.: Les grandes hematuries chez les rétrécis, Presse méd. **35**:273, 1927.

61. Demel, Rudolf: Zur Kasuistit einer seltenen Ursache von Harnröhrenblutung, Ztschr. f. Urol. **20**:125, 1926.

following treatment of the underlying infectious condition. In the male urethra, the small growths usually occur in the region of the verumontanum and the internal sphincter. Both the small and the large tumors respond readily to fulguration or snaring. Those which occur in the posterior urethra of the male may be pedunculated and occasionally interfere with the closure of the internal sphincter; those which occur near the external orifice are generally flat and sessile. Multiple and extensive growths are occasionally seen.]

McCarthy, Ritter and Klemperer [62] undertook an extensive study of the verumontanum with special reference to the ejaculatory ducts. Their aim was to answer two questions: 1. What is the precise course taken by the ejaculatory ducts through the verumontanum and prostate? 2. Does an edematous or infiltrative closure of the lumen of the duct exist in a considerable number of cases?

Eighty specimens were studied; twenty were studied histologically. The ejaculatory ducts make a sharp dip through the verumontanum from the urethral orifice at an angle of approximately 45 degrees to the urethral floor. For the first millimeter and a half the ducts diverge and then converge for the next millimeter or two, until there is a thin septum of fibrous and elastic tissue separating them; this is easily penetrated, even though soft instruments are used. They then run parallel to each other and usually at a less acute angle through the prostate gland ending at the termination of, or within, the substance of this gland. At their division into the ampulla of the vas deferens and the duct of the seminal vesicles they are further away from the urethral floor.

The lumen of the duct of the seminal vesicle is 4.5 mm. in circumference, whereas the lumen of the ampulla of the vas deferens has a circumference of 3.1 mm.; the circumference of the ejaculatory duct is noted at its termination; these measurements may be somewhat confusing. The similarity in size of the lumen of the ejaculatory duct with that of the duct of the seminal vesicle is accounted for by the fact that the ampulla opens on the mesial superior aspect of the ejaculatory duct.

The authors conclude as follows:

> We feel that an explanation of the physiological fact that the seminal vesicles are distended when solutions are injected either through the vas deferens or ejaculatory duct is of utmost interest and importance.
>
> 1. The seminal vesicles are distended when fluids are injected through the vas deferens because:
>
> (*a*) The normal resistance of the walls of the ejaculatory duct, which lumina become gradually smaller as they approach the urethral floor, causes the liquids to flow toward the seminal vesicles.

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62. McCarthy, J. F.; Ritter, J. S., and Klemperer, Paul: Anatomical and Histological Study of the Verumontanum with Special Reference to the Ejaculatory Ducts, J. Urol. **17:1**, 1927.

(*b*) A large muscular organ (the prostate) surrounds the ejaculatory duct and offers resistance to their distention.

(*c*) The ejaculatory duct has no musculature of its own to overcome the resistance of the prostatic musculature.

(*d*) The lateral wall of the duct of the seminal vesicle contains elastic tissue which is less resistant to distention than muscle tissue.

2. The seminal vesicles are distended when solutions are injected by way of the ejaculatory duct prior to any solution appearing in the vas deferens because:

(*a*) The duct of the seminal vesicle is a direct continuation of the ejaculatory duct.

(*b*) The lateral wall of the duct of the seminal vesicle contains elastic tissue and is therefore less resistant and more readily distended than the ampulla of the vas deferens.

(*c*) The lumen of the ampulla of the vas is surrounded by thick muscle walls and its orifice opens supero-mesially into the ejaculatory duct.

(*d*) The lumen of the ampulla contains several valve-like protecting folds within its lumen which tend to obstruct the entrance of any fluid into the vas deferens.

Redi [63] reported a case of rupture of the penis following trauma. Applications of ice and immobilization in cardboard tubes effected cure in a few weeks. There were no sequelae. The points of resistance of the distended organ, albuginée propre, fascia of the penis and traverses lamelliformes, being reduced to extreme thinness, are likely to break under the influence of obliquely acting forces. The symptoms are pain, deformity, swelling and extravasation of blood. The fracture is easly distinguished from contusion, on careful palpation. The prognosis must be reserved on account of possible complications; suppurative hematoma, gangrene in case of intact urethra and anuria, infiltration of urine and phlegmon, in cases in which the urethra is torn. The scarring itself may also bring about the formation of pseudarthrosis, in certain cases rendering coition impossible.

There are two methods of treatment: (1) the surgical method to which certain surgeons resort in every case and which consists in a large opening of the hematoma and suture of the corpus cavernosum and fascia with immobilization; this method is effective, but should be used only in cases in which the hematoma is extensive and offers little hope of spontaneous resorption; (2) if the hematoma is circumscribed, application of ice, immobilization and carefully performed catheterizations will often bring about cure; if the urethra is ruptured, the prognosis is more serious; a permanent catheter will be necessary, and if this is unbearable to the patient, external urethrotomy with a plastic reconstruction of the penis is necessary.

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63. Redi, Rodolfo: Un cas de fracture du pénis, J. d'urol. méd. et chir. **22**: 36, 1926.

GENERAL UROLOGY

O'Conor [64] described the use of modern cold lamp illuminating instruments in urologic diagnosis and surgical treatment. O'Conor finds that he obtains valuable information as to the size and degree of infiltration of tumors of the bladder in women by placing the lamp in the vagina and a cystoscope in the bladder, the light of the cystoscope being disconnected. The same procedure may be of advantage in the fulguration of growths in the trigone of the bladder. In man, the scope of the method is limited.

In operations on the bladder, transillumination also is useful in cases of new growth and of diverticula, while in operations on the kidney the lamp may be of value in demonstrating calculi in the renal pelvis.

Hyman [65] reviewed the urologic condition in 150 children. He believed that diseases of the urinary tract in children are more common than he had hitherto been led to believe. With few exceptions the lesions encountered are as varied as in adults. In children anomalies of the urinary tract are the underlying factors in a large proportion of the cases in which pyuria develops. This is especially true of vesical pyuria so that in any case of urinary infection in the young the existence of an anomaly should be seriously considered. The tendency among practitioners is to designate pyuria either as pyelitis or cystitis. Many of the cases in this series would undoubtedly have been overlooked had not these patients been subjected to cystoscopic and roentgenographic examination. The feasibility and safety of cystoscopy in the young are amply illustrated by a study of these cases. The proper application of present-day methods of examination will seldom make it necessary to resort to exploratory operation on the urinary tract for diagnostic purposes. A more general application of cystoscopy will make diagnosis possible early in the course of disease, before vital organs are irreparably destroyed and life endangered. The diagnosis should be made in the cystoscopic room and not at necropsy, as happens too often in diseases of the urinary tract in children.

Lowsley and Butterfield [66] pointed out the prevalence of urologic diseases among infants and children. They reviewed 100 cases that illustrate a range of urologic diseases and include most urinary diseases found in adults. They demonstrated that complete urologic examination of every child suffering from urinary disease of long standing is possi-

64. O'Conor, V. J.: The Value of Transillumination in Surgery of the Urinary Tract, J. Urol. **16**:459, 1926.

65. Hyman, Abraham: Clinical Aspects of Surgical Diseases of the Urinary Tract in Children, J. Urol. **16**:259, 1926.

66. Lowsley, O. S., and Butterfield, P. M.: Urologic Conditions Among Children, J. Urol. **16**:415, 1926.

ble at any age, by the use of modern instruments, and that such examination should always be made. As cystoscopy in young children must be done under general anesthesia, it is most important to complete every other phase of the examination before it is undertaken. If cystoscopy is carried out it should be complete in every detail, including divided specimens of urine for bacteriologic, chemical and microscopic examination, inoculation of animals, phenolsulphonphthalein and other functional tests, together with roentgen-ray examination and pyelography when these are indicated. Rarely does severe reaction follow cystoscopy and ureteral catheterization in these very young subjects; it is much less frequent than in adults. Renal tuberculosis is much commoner in children than is ordinarily believed, and may be accompanied by secondary infection.

Nonoperative treatment should be the rule whenever possible, operation being resorted to only in cases of dire emergency in children under the age of 4 years. Operative repair of congenital lesions, such as hypospadias, epispadias and undescended testicle with its accompanying hernia, should be performed only after the child has reached the age of 4. Congenital malformations causing obstruction to proper urinary drainage of any part of the urinary tract should be relieved as soon as it is discovered.

Beer [67] pointed out some analogies between the urinary and biliary tracts. In comparing cholesteremia and uricemia he showed that cholesterol is a more or less specific hepatic excretion, while uric acid bears a somewhat similar relation to renal function. By experimental feeding, both substances can be increased in the blood and in the urine. In certain conditions, such as the postinfective period in typhoid fever, the blood cholesterol is increased, while in other conditions, such as the crisis in pneumonia, the uric acid content of the blood is increased. In bilateral renal obstruction, the uric acid is the first component to be increased in the blood. In choledochus obstruction, one of the first signs is accumulation of cholesterol in the blood.

In regard to lithiasis striking analogies are discerned. The stasis or primary cholesterin stones are compared with uratic calculi which are presumed to be performed without the agency of gross infection from "a temporary spilling over of the stone material, or an increased excretion which may contribute to produce the colloidal instability that leads to the precipitation of the stones." When infection sets in a totally different type of stone occurs. In the biliary tract, the cholesterin-pigment calcium stones are found, and in the urinary tract, the phosphate stones.

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67. Beer, Edwin: Analogies Between the Biliary Tract and the Urinary Tract, Ann. Surg. **84**:517, 1926.

In regard to infection, it is striking to see how readily the bacteria are passed through these glands without apparent injury to the parenchyma. This transit through the two systems seems to leave no permanent injury unless foreign bodies or obstructive conditions obtain, and then local inflammatory changes may be induced. A comparison of the bacillary and coccic infections of the kidney and liver is made. Beer quotes Naunyn, Aschoff and others as believing that acute hepatitis, somewhat analogous to acute pyelonephritis, may be frequent, and he feels that some of the changes of the cirrhotic liver are developed in some way analogous to the repeated infections of the renal parenchyma which lead to the peculiar scarred kidney in long standing cases of pyelonephritis.

[ED. NOTE.—It is interesting to consider Beer's comparisons of these two great systems. It has been shown experimentally that increased excretion of oxalates from the kidneys may produce lithiasis, and for many years Naunyn and his followers have held that hyperexcretion of cholesterin is responsible for the production of biliary calculi of the pure pigment type. Beer's observation that typical attacks of biliary and renal colic may occur without evidence of either stone or gross inflammation is timely, as many surgeons and urologists are puzzled by these occurrences, which are baffling from the standpoint of treatment.]

Jullien [68] observed that abdominal distention in the fetus is an extremely rare cause of dystocia. He cited a case in which, after delivery of the head, the body could not be delivered until the abdomen of the fetus was punctured and 3 liters of urine withdrawn. The cause of the retention was obliteration of the urethra. The remaining abdominal organs had been retarded in their development.

Lagemann [69] described a case of a malingerer with apparent chyluria. The patient, a man, aged 40, had milky urine following an attack of influenzā. The temperature was 39 C. and the patient appeared to be ill. The milky urine contained 14 per cent albumin and also casein. The phenomenon was noticed for twenty-two days, the appearance of the urine varying from milk-white to complete clarity. Following ureteral catheterization the turbidity disappeared. On the wall of the bladder were many membranous shreds, although the mucous membrane appeared entirely normal. It was finally concluded that the patient had secretly injected milk into his bladder.

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68. Jullien, F.: Dystocie grave par retention d'urine chez le foetus, Rev. franç. de gynéc. et d'obstét. **21**:24, 1926.

69. Lagemann, Clemens: Ein Fall von künstlich erzeugter Chylurie, Arch. f. klin. Chir. **139**:240, 1926.

Randall and Muschat [70] reported the results of their study on the hydrogen ion concentration of the various secretions of the urogenital tract.

Acidification of the urine is an important problem in urologic surgery. Acidity is desirable from two points of view, but for one and the same purpose. Most secondary infections of the urinary tract are due to the colon bacillus. This organism suffers marked inhibition in growth when the reaction of the urine is markedly acid, at or below p_H 5.5. Rendering the urine acid and bringing it to p_H 5.5 is a good method of counteracting the invasion and growth of the colon bacillus. Many substances have been advocated and are in use for this purpose, those most frequently used being sodium benzoate, ammonium benzoate, acid sodium phosphate and ammonium chloride. They found that of these, ammonium chloride was more constant and stronger in its action than the others.

Their study of the influence of hydrogen ion concentration on the activity of the spermatozoa indicate that the reaction of the environment of the spermatozoa plays an important part in the physiologic mechanism involved in impregnation. The maintenance of a weak alkalinity in the genital tract in the female is of utmost importance, and cases of sterility should demand such study. The vaginal secretion is weakly acid, but the cervical secretion is almost neutral and it is assumed that the uterine secretion is probably weakly alkaline, meeting the vital requirements of the spermatozoa and probably stimulating them to great activity as they progress into this more favorable environment. Their work also shows that inflammatory conditions do not influence the reaction of the prostatic secretion, which remains as in the normal, that is, p_H 7.3, and, thus that such conditions do not play any part in changing the function of these secretions.

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70. Randall, Alexander, and Muschat, Maurice: Hydrogen-ion Studies on Various Secretions of the Uro-genital Apparatus, J. Urol. **16**:515, 1926.

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